VOICE OF THE PATIENT

A summary of the Externally-Led Patient-Focused Drug Development Meeting (EL-PFDD) on Hypophosphatasia

Public meeting: November 15, 2022 - Report submitted: April 21, 2023
Hosted by: Soft Bones, Inc., The U.S. Hypophosphatasia Foundation

Soft Bones
Finding the Key to HPP

This report is dedicated to the courageous patients, caregivers and families impacted by HPP.

Authors:

This report was submitted and prepared on behalf of Soft Bones. Input was provided by Deborah Fowler (Soft Bones President and Founder), Denise Goodbar (Soft Bones Executive Director). Soft Bones contracted with consultant Trista Dawson Rutledge for assistance in writing this report.

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Thank you to Larry Bauer, RN MA and James Valentine, JD MHS, for providing invaluable guidance and support. Hyman, Phelps & McNamara, P.C. is a law firm that works on FDA-related issues in drug development as well as with patient advocacy organizations to help bring the patient voice to drug development and review.

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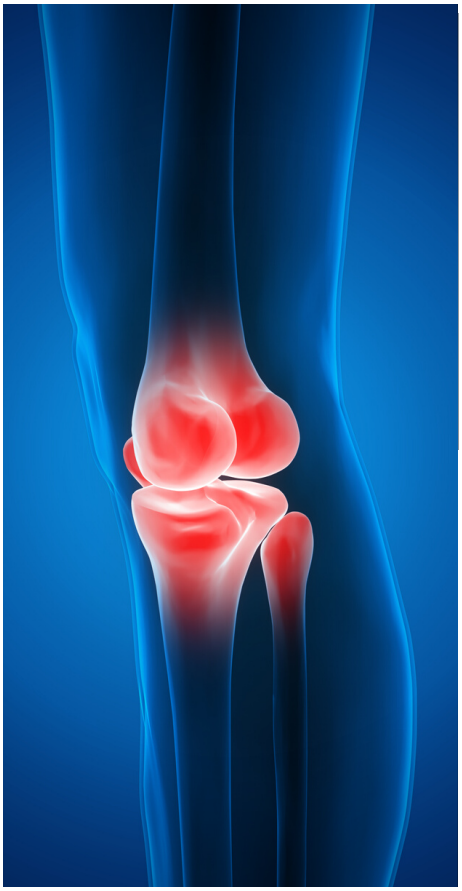
Executive Summary

Hypophosphatasia (HPP) is a rare, genetic and potentially life-threatening metabolic disorder. People with this condition have low levels of the enzyme alkaline phosphatase (ALP), or more specifically tissue non-specific alkaline phosphatase (TNALP), which affects the development of bones and teeth. However, symptoms can vary greatly between patients and include a range of disabling physical and mental health conditions. Patient symptoms may include intense and constant pain, brain fog, fatigue, restricted mobility, frequent fractures, depression and anxiety, among other ailments. More severe types of HPP are often diagnosed in utero and can be fatal, leading to stillbirths or children not surviving past one year of age.



There is currently no cure for HPP. One FDA-approved treatment is available, which is an enzyme replacement therapy called Strensiq® (asfotase alfa). This treatment can help improve some symptoms but requires frequent, painful injections and can cause potentially serious side effects.

On November 15, 2022, Soft Bones convened an Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting on HPP. The goal of this meeting was to enable the FDA and other important drug development stakeholders to hear directly from patients and caregivers about their experiences with HPP. Perspectives were shared about HPP symptoms and the impact on their daily lives, as well as current approaches to treatment and hopes for future treatments.

The expert presentations, patient and caregiver video stories, panelist discussions, caller remarks, meeting polling data and comments submitted online during and after the meeting provided the content for this “Voice of the Patient” report. Although the meeting was based in the U.S., feedback was provided by participants globally.

Patients and caregivers participating in the meeting outlined the extremely challenging and varied symptoms of HPP, the profound impact of HPP on daily life and the critical need for new treatment options. Several themes emerged from the meeting which are summarized below and explored throughout the report.

Key Meeting Themes

1. HPP has been called "the bone disease with the greatest spectrum of severity" with symptoms varying greatly between patients, including family members

- Although HPP is characterized by low levels of the enzyme alkaline phosphatase which affects development of bones and teeth, patients with HPP experience a broad range of debilitating and serious physical and mental health conditions
- Severity of HPP symptoms varies widely, including within families, making it extremely difficult to plan for the journey ahead for each patient
- HPP can be fatal, leading to stillbirths or children not surviving past one year of age; in other cases, children can live into the toddler years but then succumb to respiratory infections such as pneumonia (including those on enzyme replacement therapy)

2. HPP can cause intense and relentless pain along with a range of often severe physical and mental health conditions, all of which can profoundly impact daily life

- Many patients with HPP face debilitating, chronic pain (including in bones, joints, muscles), mobility issues, brain fog and fatigue, frequent broken bones, and dental issues, among other ailments
- HPP can negatively impact all fundamental aspects of daily life including sleep and exercise, as well as the ability to socialize and maintain a career or go to school
- Patients often go to great lengths to adapt or adjust their lifestyle to cope with severe symptoms and as a result may have a greatly reduced quality of life

3. Life with HPP can be unpredictable which creates enormous fear and uncertainty for the future

- Living with intense, unpredictable symptoms can lead to depression, anxiety and in some cases, thoughts of suicide
- The stress, fears and anxiety for the future often impact the family unit as whole
- Many patients worry about potentially losing independence, becoming unable to be the parent or spouse they want to be or burdening their families
- Parents are concerned for what the future looks like for their children with HPP who may deal with worsening pain and other symptoms, the negative mental health impact and the inability to lead a "normal" life

4. Current enzyme replacement therapy can only improve some HPP symptoms but requires frequent (up to 6X/week), intensely painful injections with potential serious side effects and cumbersome temperature requirements

- The HPP community is grateful for the "game-changing" enzyme replacement treatment which can improve some symptoms but it comes with significant challenges
- Painful injections have been described as feeling "like fire" and can cause lipodystrophy, skin scarring and bruising; some patients voiced concerns about "running out" of injection sites
- There are questions about the efficacy of enzyme replacement therapy when injected into areas where patients have lipodystrophy
- Many parents need to physically restrain children to inject, with some children developing an intense fear to the mere sight of the medicine
- Serious reactions are possible, with one patient recalling traumatic post-injection episodes where he couldn't breathe and felt as if he was dying
- Many patients and caregivers question the impact of long-term elevated alkaline phosphatase levels
- Travel is extremely stressful or difficult, or not possible at all, due to the refrigeration requirements

5. Patients and caregivers are desperate for a disease-modifying treatment that can alleviate HPP symptoms and slow progression, with a less painful administration

- Currently no treatments alleviate all HPP symptoms or impact the trajectory of disease progression
- Due to the heavy emotional and physical toll of painful injections, there is an urgent need for a treatment that is easier to administer, particularly important for children with HPP
- Without a disease-modifying treatment, many patients with HPP will continue to suffer with intense physical and mental health conditions, and a severely impaired quality of life

Introduction

The Externally-led Patient-Focused Drug Development (EL PFDD) meeting on hypophosphatasia (HPP) was held on November 15, 2022. The PFDD initiative by the FDA grew out of the realization that patients, families and caregivers, along with associated patient groups, are experts in living with their condition and are uniquely positioned to inform therapy development and evaluation.

The information gathered at the meeting and summarized in this report may impact decisions regarding drug development and review, and may ultimately improve the overall quality of life for patients living with HPP.

The EL-PFDD meeting was organized by Soft Bones, Inc., the U.S. Hypophosphatasia Foundation. This organization provides valuable information, education and support for people living with HPP, their families and caregivers. With a vision of a world free of HPP, Soft Bones works to unite the global HPP community and collaborate closely with researchers and clinicians to advance the scientific understanding of the disease.

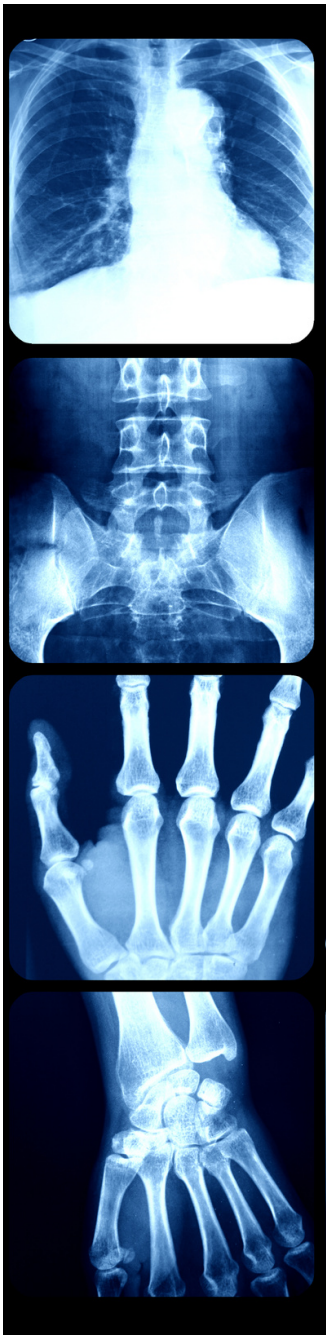
Overview of HPP

Hypophosphatasia (HPP) is a rare, heritable, and sometimes life-threatening metabolic bone disease.

Affected people have low activity of the enzyme alkaline phosphatase (ALP), or more specifically the tissue non-specific form (TNSALP), which can thereby impair skeletal and dental mineralization. Without adequate TNSALP, bones may bend or break easily and heal slowly and teeth can fall out. However, what patients experience on a daily basis often goes far beyond these symptoms.

Some consider HPP “the bone disease with the greatest range of severity.” Rare severe types of HPP can be fatal with stillbirth or not surviving past one year of age because of skeletal weakness and deformity. Symptoms and further complications can vary significantly between patients, even family members, and include a range of sometimes disabling health conditions. Many patients describe intense and constant pain, often going to great lengths to adapt or adjust their lives. Fatigue, restricted mobility, depression and anxiety are other difficulties that may impact their lives.

> **Within 4 years we saw over 11 specialists, received 21 diagnoses and we were prescribed 32 medications. None of which took away her pain and fatigue.**
>
> Wrote Sherri, who lives with HPP, and has a child with HPP



Diagnosis of HPP generally is made by an experienced physician through a combination of patient medical history and physical examination together with x-rays and blood and genetic tests. The disease is classified based on the age at which complications first appear. The five main types of HPP, in order of increasing severity, are as follows:

Odonto (most mild form; can occur in childhood or adulthood): symptoms include dental abnormalities such as teeth falling out early and easily; no skeletal pathology

Adult: featuring slowly healing fractures, along with a range of symptoms due to chronic disease

Childhood (diagnosed after 6 months of age): skeletal disease, premature loss of “baby” teeth, short stature, delayed walking, craniosynostosis

Infantile (diagnosed before 6 months of age): if untreated, fatal in about 50% of patients within the first year of life; symptoms include skeletal disease, failure to thrive, hypotonia, and seizures

Perinatal (diagnosed at birth/in utero; most severe form): very often stillbirth with deformed limbs and respiratory compromise

While the exact prevalence of HPP is not known, it is estimated that one of every 300 Americans may be carrying a mutation in the *ALPL* gene underlying HPP. It is estimated that the lethal forms of HPP occur, from the presence of two copies of an *ALPL* mutation, in approximately one of every 100,000 live births. HPP affects all races, although it seems especially rare in Black ancestry.

Currently, there are about 450 known *ALPL* mutations with inheritance of HPP being autosomal recessive for the severe forms, and either autosomal recessive or autosomal dominant for the mild forms. However, a genetic diagnosis is currently not a precise predictor of HPP severity. More research is underway in this area, including studies sponsored by Soft Bones.

There is currently no cure for HPP. Previous treatment approaches included experimental infusion of alkaline phosphatase rich plasma or bone marrow cell transplantation for life threatening disease, and “off-label” use of a form of parathyroid hormone called teriparatide (marketed as Forteo®) for affected adults, all with limited success. In 2015, an enzyme replacement therapy (asfotase alfa, marketed as Strensiq®) was approved multi-nationally, including by the FDA, typically for pediatric-onset disease.

Meeting Overview

This meeting was designed to highlight patient and caregiver experiences around living with HPP, the impact of disease symptoms on their daily lives, as well as their perspectives on available treatment approaches and hopes for future treatments (agenda and discussion questions are shown in Appendix 1).

The meeting began with opening remarks by co-moderator Deborah Fowler, President of Soft Bones and mother to her son Cannon who was diagnosed with HPP at 18 months. She welcomed participants and highlighted the importance of the meeting and participation from the HPP community.

Dr. Patricia Beaston from the Offices of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research (CBER), emphasized the FDA’s commitment to understanding the patient experience and impact of diseases such as HPP, as well as patients’ perspectives on benefits and risks of treatments, and participation in clinical trials. Dr. Michael P. Whyte from the Washington University School of Medicine, Shriners Hospitals for Children provided a medical overview of HPP, showing the complexities of the disease and wide-ranging severity faced by patients.

James Valentine, JD MHS, who helped launch the PFDD program at the FDA, served as co-moderator and outlined the meeting format and guidelines.

Both the morning and the afternoon sessions included powerful pre-recorded video submissions from patients and caregivers who were selected to provide a range of experiences (Appendix 2). The video stories were followed by a discussion with a pre-selected live panel covering various topics. Meeting viewers were encouraged to provide their perspectives by joining via phone or submitting written comments online. Participants who were HPP patients or caregivers were periodically invited to respond to live polling questions (by using phone, computer or tablet) to provide demographic information and experiences. Caregivers were instructed to respond for patients currently under their care or for those who may have passed away from HPP complications.

Nearly 200 people joined the live webcast, including more than 62 people living with HPP and 27 caregivers/parents, with 83 participating in the polling questions.

The meeting concluded with a summary provided by Larry Bauer, RN MA, a former member of the FDA Rare Diseases Program, and closing remarks from Deborah Fowler and James Valentine.

Members of the HPP community were invited to submit written comments both during the meeting and in the 30 days following, which were incorporated into this report.

A recording of the HPP EL-PFDD meeting in its entirety can be found here: https://softbones.org/el-pfdd/.

Meeting participants

Demographic polling questions (Appendix 3) revealed the following about the polling audience:

- Approximately two-thirds were people living with HPP (66%) and one-third were caregivers to someone with HPP (34%)
- Majority identified as female (80%) from the ages of 51-70 (56%) and 31-50 (22%)
- Most joined from the U.S. Eastern time zone, although there was representation from other major U.S. regions as well as from other countries
- Childhood HPP was the most common type of HPP (49%), followed by infantile (26%), adult (14%), perinatal (2%) with some being unsure of the specific type of HPP (9%)

Report Overview

This Voice of the Patient report intends to support the FDA's understanding of the burdens of HPP on patients and caregivers, and their perspectives on current and future treatments. This input may also be of value to the drug development process more broadly, may help inform clinical trial design, and may support the review of future therapies for HPP.

This report aims to summarize the input graciously provided by patients and caregivers during the EL-PFDD meeting and is not meant to represent in any way the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other aspects of HPP that are not included in the report.

> **What frustrates me most about HPP is the constant state of unknowns that the diagnosis carries, especially because every individual is affected differently in regard to their level of severity, even if within the same family composition**
>
> said Laiken, mother of two young boys with HPP

The first discussion topic focused on patients' and caregivers' experiences with HPP symptoms and the impact on their daily lives.

A number of personal and powerful video submissions were shared to start the session (Appendix 2) from three people living with HPP and two caregivers, along with two people who were both caregivers and patients themselves. A panel then discussed experiences related to symptoms and the impact of HPP, with others calling in and moderators highlighting select submitted comments. Panelists and participants described a wide range of debilitating and disabling symptoms, most of which profoundly impact their daily lives.

Most Significant HPP Symptoms

The symptoms of HPP vary greatly, even among family members, which was reflected in the panelist stories and audience discussion. Audience polling indicated a wide range of symptoms, with pain cited as the most often experienced symptom followed by walking/mobility issues, skeletal issues, losing teeth, brain fog/fatigue, sleep disturbance and mental health effects (Appendix 4, Question 1). The panelist and audience discussions validated these responses and provided insights into the heterogeneity of symptoms.

Top HPP-related health concerns*

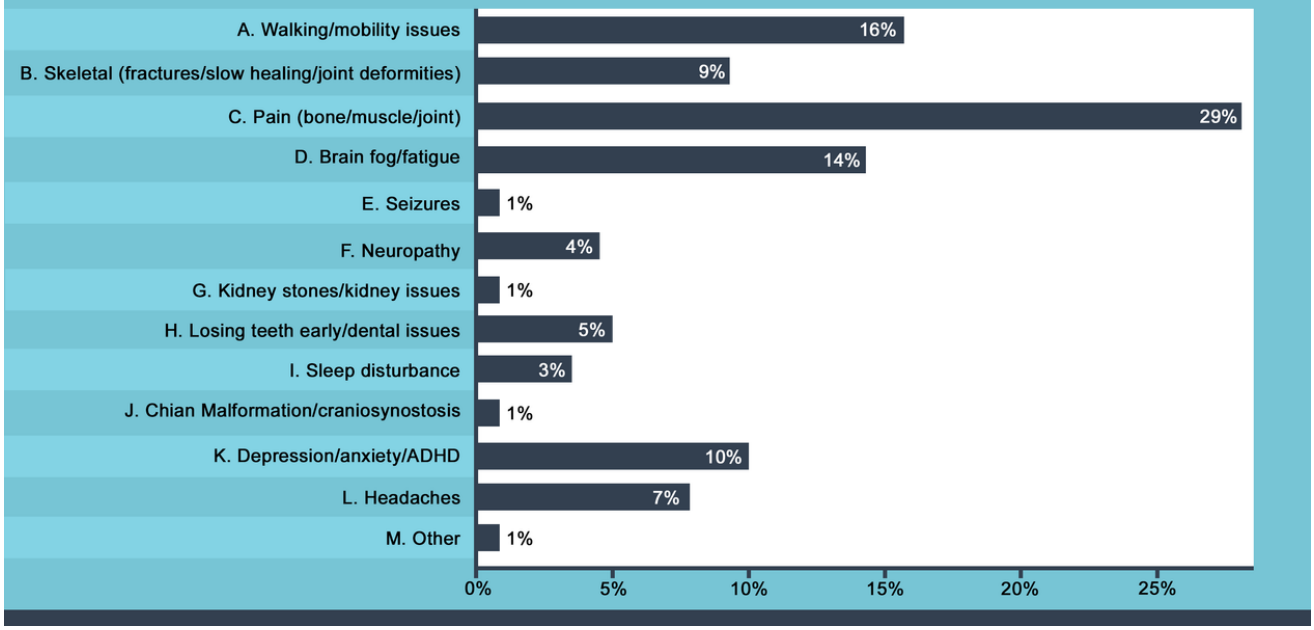
- Pain (bone/muscle/joint)
- Brain fog/fatigue
- Walking/mobility issues
- Skeletal (fractures/slow healing/joint deformities)
- Losing teeth early/dental issues
- Sleep disturbance
- Depression/anxiety/ADHD
- Headaches

* Topics that received > 9% responses from polling participants; see full results in Appendix 4, Question 1

Intense and excruciating pain

Throughout polls and audience discussion, it became apparent that a central issue to many people living with HPP is severe and debilitating pain. When asked about the most troublesome symptom for patients (Appendix 4, Question 2), pain rose to the top of the list.

Select the most troublesome hypophosphatasia-related health concerns that you or a loved one have ever had (select top 3)



> **By the end of sixth grade, she was a shell of the child she used to be. She rarely left her room and when she did, my husband had to carry her due to the pain she had in her legs. She didn't want to live the life she had.**

said Sherri, talking about her daughter with HPP

This finding aligned with Deborah Fowler's welcome remarks where she noted that the HPP patient community is experiencing a concerning amount of unreported pain, with many patients often going to great lengths to adapt or avoid pain altogether. This was echoed throughout the discussions around the topic. The narratives shared by participants provided additional insight into the extent and intensity of pain they experienced.

Suzanne, who lives with HPP, wrote about the varied nature of the pain and inability to escape it: "There are so many kinds of pain. Muscle pain, bone pain, joint pain, overall pain.... So much pain it's overwhelming. Treating it with pain meds is just chasing it. Nothing works. It ends up chasing you. You can't get away from it."

Others talked about the intensity of the pain itself. Suzy, living with HPP, said: “It feels like our legs are on fire,” while her twin sister Amy, who also has HPP, said: “The pain and lack of hope were unbearable.” Jennifer shared a similar sentiment: "As a patient living with HPP, I can vouch that the bone pain is excruciating” with Nellie describing her pain due to HPP as “deep to the bone.”

There is no day without pain

wrote Mel, who lives with HPP

In the past five years, I've gone from being able to hike five kilometers to not being able to walk 500 meters and now being in a wheelchair part-time

wrote Taylor who lives with HPP

Disabling walking and mobility issues

A delay in walking is a typical symptom seen in children with HPP, although patients of all ages can struggle with mobility issues. While some patients may need to limit physical activities, others may require the use of a wheelchair or other device. Many parents noted a delay walking for their children with HPP, while adults with more severe disability talked about not being able to walk for more than a few minutes.

Aaron noted details around the drastic downturn in his mobility in his teen years due to HPP after being a very active child. At 18, he was using a walker and he had a hip replacement at 20 and then again at 24. As he said: “The pain and mobility is extremely bad and it makes some days very hard.”

Wendy wrote that she had been a highly active person but as the symptoms of HPP came on at age 45: ”I could not walk on uneven terrain, walk against a gentle wind, or make it up the slightest incline.”

Christine shared the heartbreak of seeing her 17-year-old son with HPP struggle with mobility: "Something that we took for granted is simple walking, going up and down stairs. By the time he was 11 years old, it was like he was a 90-year-old man. Watching your child be debilitated in front of your eyes is hard.”

Incapacitating brain fog and fatigue

Difficulty concentrating, memory issues and feeling sluggish can be part of having “brain fog” and can be accompanied by incapacitating fatigue. Some patients noted that while they could adjust their lifestyle to try to lessen other symptoms (such as avoiding walking or standing for too long), one woman living with HPP said that there was no way to avoid the brain fog and fatigue while another tried to cope by planning her daily activities around her fatigue.

The debilitating effect of this fatigue also affected younger adults with HPP. Maya, an 18-year-old living with HPP, reflected on her time in school: “I struggled every day to either go to school or to stay at school. I was falling asleep in class. The fatigue I felt was so overwhelming.” Richard wrote about how the fatigue caused by his son’s HPP took away activities that brought him joy: "My son's pain and fatigue impact his mobility and his brain fog make it impossible to drive or do the things he loves, like reading and playing the piano and guitar."

Suzanne talked about the brain fog and fatigue led to frustration and shame: “For as long as I can remember I've thought that I am not as smart as I am. I've been so ashamed trying to hide the fact that my brain was not engaging as it should.”

Others with HPP talked about the challenges in completing even simple tasks. Wendy said: “What used to take me 30 minutes, it might be a week,” while Scott shared that: “I have to fight even harder to try to get through the bouts of fatigue…not being able to continue with a task that I want to accomplish.”

I wake up as tired as when I went to sleep

wrote Kyle, who lives with HPP

Frequent Bone Fractures

Although HPP extends far beyond bone issues, the defective skeletal mineralization which results in softening of the bones is a defining feature of the disease. Participants talked about experiencing multiple broken bones (which can begin to happen in utero), spending months in casts and undergoing countless surgeries while parents often modify their children's activities in fear of potential fractures.

Jessica wrote that her young daughter with HPP was born with "toothpick-like bones" while Jennifer, who has HPP along with her three daughters, emphasized the fragility of her bones, noting that she's had more than 40 broken bones while one of her daughters has already had 27 broken bones.

Sally, who lives with HPP, talked, about our countless fractures: "I can't tell you how many metatarsal, tibia, fibula, elbow shoulder fractures I've had. My doctors, I've had many, would always get little tears in their eyes and be like, 'Oh no, not again. We got another fracture we have to deal with.'"

Early loss of teeth and dental issues

Alkaline phosphatase is important for normal tooth development. With low levels of this enzyme in people with HPP, tooth loss is a commonly observed complication due to deficient cementum formation. Teeth can fall out early (between 1 to 2 years of age) and easily, often with the entire root intact.

Some people with HPP reflected on past dental issues which, in retrospect, were due to HPP: "When I was growing up, every time I went to the dentist I'd have 16 cavities and they thought it was because I was eating too much candy," said Pat who lives with HPP. While Laura recalled early tooth loss, noting that she lost all of her upper and lower teeth before four years old.

> **After a small fortune spent on dental work and hundreds of hours spent in dental chairs over my lifetime, I will still lose my teeth**
>
> wrote Gretchen, who lives with HPP

My grandmother had HPP and she committed suicide from the pain of the disease and the progression of it….so I have great concern about what the progression of the disease looks like in the future

said Nellie, who lives with HPP

I remember feeling suicidal when I was eight years old

said Jennifer, living with HPP

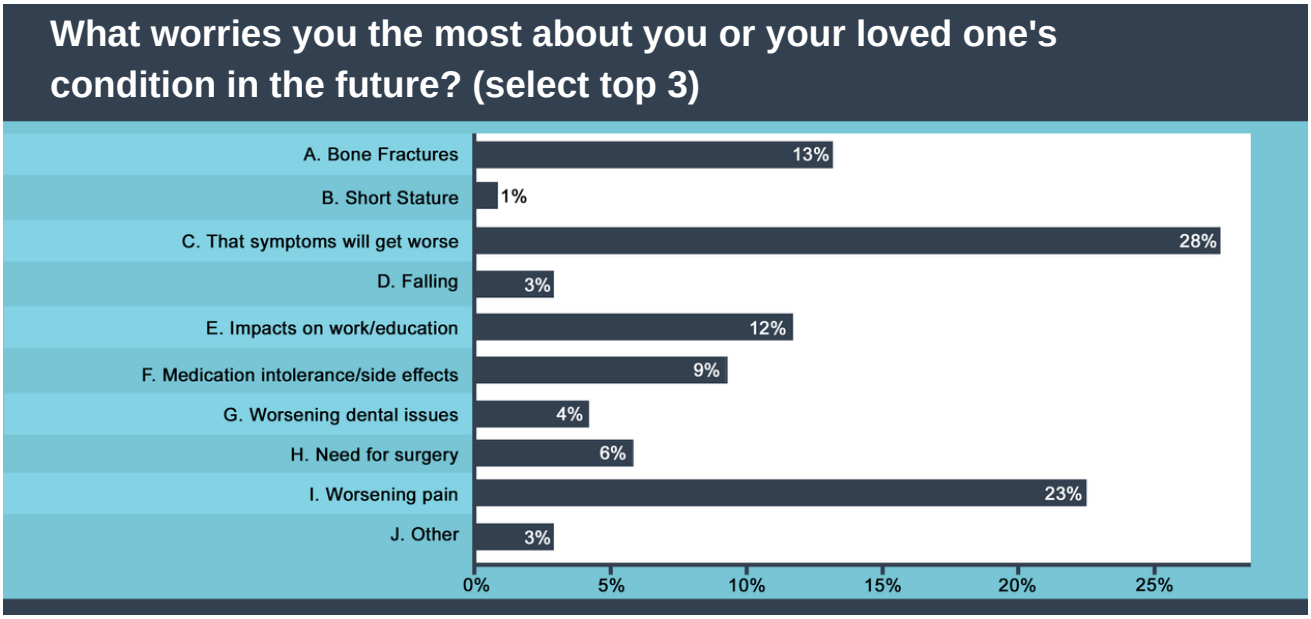
Serious emotional and mental health conditions

Many of the patients and caregivers talked about the heavy emotional and mental toll of HPP. They grapple with anxiety around the disease itself and the impacts on daily life as well as fear and uncertainty for the future. Examples were shared again and again around the significant and severe impact on mental health, including depression, anxiety and even thoughts of suicide. Suzy, who lives with HPP, said: “Depression and anxiety added layers to an already difficult diagnosis journey,” while Maya, who is 18 and living with HPP, said: “My mental health continued to get worse…I've been totally isolated.” Amy shared that how serious the mental health effects can be: “When I first learned that we had HPP, I wondered if the leading cause of death among HPP patients was suicide.”

Becky, mother to a young daughter with HPP, talked about the deep emotional impact on her young daughter: “Juliana also suffers from medical PTSD. Sometimes it rears its ugly head after a painful injection or a doctor visit and it's always present before and after a surgery. We can always see a PTSD rage coming when she starts quietly and systematically tearing her room apart. I have learned that the best thing to do is stay close and when she is ready, just wrap her in my arms and let her cry it out.” Autumn shared that her young daughter also struggles with the aftermath from medical procedures: “One of the hardest symptoms of HPP was the craniosynostosis that developed and the surgery that was needed because of it. It has created long-term anxiety for my daughter at the doctor's which makes it difficult to take her to appointments.”

Disease Progression & Worries for the Future

Like the symptoms of HPP themselves, the rate of progression is highly variable over the course of a patient’s life. This uncertainty around the future can bring great concern and worry for patients and their loved ones. A participant poll revealed that biggest worries for the future include worsening symptoms, particularly pain (Appendix 4, Question 4). During the discussion, participants discussed that the progressive and evolving nature of HPP makes it difficult to plan for the future, with many worried about losing independence and being a burden to their family.



Ashley, whose spouse has HPP, wrote: "As a wife of an HPP patient who works as a firefighter or a paramedic, I'm most concerned about his ability to work, which is currently our only source of income. In a rare moment when he was brutally honest about his concerns, he worries about being a burden on the family." Kirsten echoed the concern: "Nobody can really tell you how it's going to progress for you and so losing your mobility and being more dependent on people is a huge fear."

Aaron talked about his worry that HPP will impact his ability to be there for his children: "The overall concern is that this will progress to a point where I can't be the father that I want to be."

Makayla, who has HPP along with her four children, expressed fears for them: "I worry how HPP is going to affect their progress both physically and mentally into the future."

She has told me repeatedly, 'Mom, I don't think I will reach my grownup hood.' That's my biggest fear too

Becky shared her daughter's fears about life with HPP

Impact on Daily Life

Participants described the physical, emotional and social toll of living with HPP. A polling question (Appendix 4, Question 3) showed the range of impact on patients from not being able to walk, run or play sports to being unable to attend work or school to missing social events and having disrupted sleep. Although everyone's experiences were unique, common themes emerged from the panelists, discussions and submitted comments which highlighted the severe consequences of the disease.

Cindy talked about the impact on basic activities: "HPP has a huge impact on my daily life. Some days I cannot wash my own hair in the shower because of the pain and fatigue," while Judith talked about her limitations: "I have a very hard time doing basic chores… grocery shopping is impossible. I fear that I can never be independent because of it."

Olivia, who is a caregiver to her mother with HPP, talked about how HPP has taken away many of the activities her mother loves: "Now its things like not being able to garden, repaint the bathroom, host a baby shower. There are lots of things that bring her joy that she struggles to do now." Wendy shared a similar experience: "My symptoms came on suddenly and ended not only my career but prevented me from doing all the activities I enjoyed and took all aspects of my life that defined my personality."

Lindsey, talked about the difficulties in finding understanding and support when many symptoms can be invisible: "I am a patient with HPP. I am also a mom to three sons with HPP. It is incredibly challenging having everyone from neighbors to medical professionals say — but you and your kids look normal — you can't have a rare disease." While Carol also wrote about the lack of understanding: "My journey was a rough one and was considered a hypochondriac by many. It was so hurtful because I suffered so."

> **HPP impacts every aspect of my day and has completely changed my life**
>
> wrote Wendy, who lives with HPP

Inability to go to Work or School

The physical and emotional impact of HPP, along with uncertainty of symptoms from day-to-day, can make it incredibly challenging for some people with HPP to maintain a career or keep up with school activities. Some patients talked about giving up beloved professions, while others harbor a fear of not being able to provide for their family. Children can struggle in school, with both the classwork and social aspects, while others talk about not fully living to their potential.

Kirsten, who lives with HPP, said: “I was a teacher for 20 years…I loved teaching. I had to stop teaching because it was constant pain. I went to try even virtual teaching and even the pain from working on the computer became so much.” While Wendy shared that: “I am now on permanent disability, which I am tremendously grateful for but I would rather be an independent and functional member of society.”

> **I am not working, nor have I ever worked at the capacity that I wish**
>
> said Debra, who lives with HPP

Richard wrote about how much his son’s life has changed due to HPP: “Mike is an intelligent guy with a graduate degree from Columbia University, yet he has been reduced to watching movies or listening to soft music in his room, every day. His quality of life has long been negatively impacted by HPP, both in terms of the quality of his activities and the limits to his activities,” wrote Richard, parent of an adult son with HPP.

Ed talked about fears around being unable to provide for his family: "It's impossible to work in the physical condition this disease puts us in. This also affects our families who rely on us to be the earners and now cannot."

Challenges in making and maintaining social ties

With the multitude of symptoms patients with HPP often face, and the variability of those symptoms from one day to the next, patients talked about the difficulties in being able to make and maintain friendships and social networks.

Kirsten spoke about her yearning to socialize yet facing stark realities due to HPP: “Because you're always in pain, you're tired and so your tolerance level sometimes isn't all that great. So you'd rather just sort of stay home. That's been very difficult for me socially.” Tracy shared a similar sentiment around keeping up social connections: “It's really difficult to maintain friendships because if somebody wants me to plan to come over next week, I don't know how I'm going to feel.’”

And for young adults living with HPP, this inability to socialize comes at a critical time in life where friendships and social networks are typically front and center. Richard wrote about his son’s struggles with HPP: " More recently his quality of life has been reduced to the level of a shut-in, which has had major impact on the family. His condition has had a profound impact on us all." Maya, 18 years old, shared that: “I'm mostly home bound. I'm still trying to get out more. But it's challenging to find friends and not feel so anxious.”

Reduced physical ability and avoidance of certain activities

Given the significant physical impacts of HPP, particularly the intense pain, persistent fatigue and reduced mobility, patients can face severe restrictions with respect to physical abilities. While some exercise can help improve symptoms, several participants noted the danger of “overdoing it.” Parents shared worries about their children participating in certain sports and have restricted activities as a result.

Chris, who lives with HPP, talked about this important balance of exercise: “Trying to be as active and as physically fit as I can be because I know that's good for me against this disorder. What I fear though, is that if I overdo it, I suffer for several days at least, if not several weeks thereafter.”

Laiken, who is the mother of two young boys with HPP, talked about modifying her children’s activities: “Due to the nature of the diagnosis and not knowing how well their bones may handle contact or impact sports, we try to promote more individual or non-contact leisure activities. This is to prevent any additional risk of fracture.” Becky mirrored this sentiment about her young daughter with HPP: “She is very frustrated that she can't play soccer or lacrosse like her friends because one accidental kick could break her leg.”

> **I had to drastically reduce what was an active life. I was able to work out almost daily. I could squat over 100 pounds. Now it's all I can do to walk around the block**
>
> wrote Donna, who lives with HPP

Disrupted Sleep

Many participants noted a substantial impact on a fundamental aspect of health – that of sleep. Some pointed to pain as a key disrupter to getting a good night's rest. This interrupted sleep then had a domino effect, resulting in brain fog and fatigue, which then went on to hinder their daily activities.

Kirsten described the effects on sleep and its subsequent impact: "I wake up multiple times a night with pain and then it affects your day because you're fatigued, then you get brain fog, you don't think or comprehend as clearly. All of the things sort of tie in together." William, who lives with HPP, shared a similar sentiment: "I feel like sleep becomes extremely inefficient and you get all the symptoms of sleep deprivation like fatigue, anxiety, and trouble thinking."

Abby talked about the challenges of getting stretches of uninterrupted sleep: "I experience significant sleep difficulties because of pain and awaken roughly every 1.5 hours throughout the night," while Melanie shared similar challenges: "It is often difficult to get to sleep due to the pain. You are easily woken up because you are often just dozing."

> **My body was in so much pain even while sleeping that I'd wake up crying. I was disappointed to wake up every morning not knowing how I could get through another day**
>
> said Amy, who lives with HPP

The second discussion topic of the meeting focused on patients' experiences with current treatment options as well as thoughts around ideal future treatments. To begin the session, four patients with HPP and one caregiver of a young child provided video testimonies which were followed by a panel and audience discussion.

It was striking that more than half of participants polled (55%; Appendix 5, Question 3) indicated that their current treatment approaches only address the most significant HPP symptoms "somewhat" with the biggest drawback being that current therapies "only treat some but not all symptoms" (Appendix 5, Question 4), illustrating the critical unmet medical need and the need for new HPP treatment approaches.

Perspectives on Current Treatments

Throughout the session, patients and caregivers shared experiences across a wide range of therapeutic interventions. According to an audience poll (Appendix 5, Question 1), the most commonly used medications or medical treatments by patients with HPP are pain medications (NSAIDs or prescriptions) and enzyme replacement therapy. Additional treatments included supplements, anti-depressants/anti-anxiety medications, sleep aides and surgery.

Despite varying levels of positive experiences and some symptom relief, overall, participants expressed frustration that there are no curative or disease-modifying therapies for HPP that can slow or stop disease progression.

Enzyme replacement therapy (Strensiq)

There was a heavy focus throughout the afternoon session discussing the successes and shortcomings of Strensiq, the only FDA-approved medication in HPP. As Deborah Fowler, president of Soft Bones, said: "For many, this has been a life-changing therapy but despite this incredible breakthrough for HPP, we still have our share of challenges." Panelists and participants shared a broad spectrum of experiences with Strensiq with some recounting how it was lifesaving while others discontinued treatment due to its inherent challenges. Others talked about the challenges with the high cost of treatment and worries if their insurance will continue to cover it.

> **Although I'm very grateful to be on Strensiq, it's far from a great solution**
>
> wrote Lara, who lives with HPP

> **Strensiq saved my life, but the pain, mobility limits, fatigue and emotional challenges remain**
>
> wrote Tracy, who lives with HPP

Benefits and burdens of treatment

Patients taking Strensiq and parents who have to administer the treatment shared how grateful they are to have a treatment and highlighted its benefits. However, its significant shortcomings became readily apparent during the discussions.

Jessica talked about how Strensiq saved her daughter's life: "Our daughter was started on Strensiq at two days old. If it weren't for this medication, she would not be with us."
A number of patients talked about the benefits to regaining some normalcy in their lives. Susan, who started taking Strensiq at 54 years old, said: "Those shots totally changed my life and every aspect of daily living for me," while Cindy echoed similar sentiments: "I never want to go back to where I was before Strensiq. I was pretty much bed-ridden, scooter bound. Until something better comes along, I don't ever want to be without my Strensiq."

However, the discussion included both the benefits as well as the challenges of Strensiq. As Amy said: "I would do anything I had to do to ensure my child survives, but Strensiq is not a perfect solution."

And while many patients continue treatment despite the challenges, others made the decision to stop using Strensiq altogether. Emily said: "I was on Strensiq for a year and a half, but my condition worsened significantly…I stopped taking Strensiq at that point," while Richard talked about his son's experience: " Injections were very painful. His symptoms worsened… after three years my son and his doctor agreed it would be best to stop treatment." Kristina, caregiver to a patient with HPP, wrote: "We have chosen to stop treatment with Strensiq for our child due to the stress of injections and side effects."

Intensely painful injections

The pain of frequent, nearly daily Strensiq injections was heard again and again from patients receiving treatment and parents administering injections to their young children.

As Cindy, who has HPP along with her two daughters and two granddaughters wrote: “The injections hurt very much going in. They burn like fire,” and went on to say that one of her granddaughters had to stop treatment because as she got stronger, her parents couldn’t hold her down sufficiently and were afraid they were going to hurt her while trying to administer an injection.

The pain of the injections for young children can be extremely challenging for caregivers –both physically and mentally. Jennifer wrote about giving Strensiq to her daughter: “Our biggest struggle is giving her the injections and the impact of the active injections on our entire young family. I'm often the only adult in my household with my husband who frequently travels for work. I cannot administer treatment without one or two other adults holding her down.”

Jessica said “It breaks our hearts every Tuesday, Thursday and Saturday having to pull up the medication and poke her yet again. She has gotten much better, but she carries so much medical trauma/anxiety with her that when we wipe her with the alcohol prep pad, she is already panicking.” Jennifer shared a similar sentiment: “2x days injections are incredibly hard for our warrior Zeke. He screams and does not want to have them. We know he needs them, and so we compassionately encourage him through these injections.” Laiken talked about her two young boys who have HPP: “We can see anxiety in the boys created by the medication , fear related to the pain of administration.”

Her siblings watch us in horror as we have to pin down their screaming sister in order to administer medication

wrote Jennifer about giving injections to her child with HPP

“Running out” of injection sites due to lipodystrophy, scarring and bruising

Participants talked about the challenges of frequent injections with many experiencing lipodystrophy, with the skin thickening or pits forming at the injection sites, as well as discoloration and scarring. As a result of the damage to the skin over months and years of treatment, many patients are challenged to find places on their body to inject the treatment. Cannon, a teenager with HPP, shared: “I am running out of places to inject because of the scarring that I have from 13 years of shots. The spots that I inject look purple and bruised. My stomach looks disfigured and looks abnormally swollen, and never goes away. I’m currently only able to inject on my thighs and my backside… and my doctor doesn’t know how much longer my thighs will hold up.”

Rebecca spoke of similar challenges with her daughter with HPP who receives 12 injections a week (Strensiq plus a growth hormone): “She has lipoatrophy on both arms. Her legs and buttocks are bruised. We're running out of shot sites.” while Richard shared insights around the impact on his son: "My son developed injection site reactions even while rotating his sites. His stomach bulged with hard knots."

Lara wrote: “I have the same problems everyone else has mentioned: painful, burning injections; huge sore, hot, red injection locations for the first four months, increasingly leather-like skin that is hard to inject and lipodystropy with purple lumps.”

Serious mental health consequences

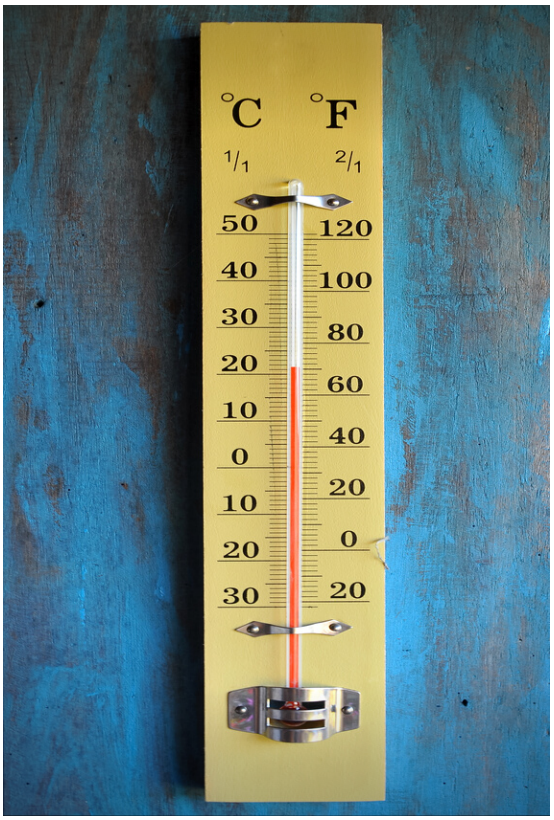
The effects of the injections extend beyond the physical impact and into patients’ mental well-being. Many reported serious impacts on the patient’s self-esteem and self-confidence, with particular difficulties for those in the teen years. One parent talked about how the injections instilled fear in her child, often triggered by the mere sight of the medicine itself.

Elizabeth talked about her 2-year-old son’s reaction: “He is very fearful as soon as he sees the orange cap needle, he starts crying because he knows he's going to get his injection.”

Rebecca shared her fears for her daughter with the teen years ahead: “As she nears the age of a teenager, I worry about those discolored and lipoatrophy areas will impact her already fragile self-confidence." The impact on self-confidence can extend into the adult years. Susan noted that she rotated injection sites over her entire body for seven years, and that: “It has left its marks of lipodystrophy in these areas to the point where wearing summer clothes, exposing my arms and legs can cause me a lot of embarrassment.”

Additional Concerns

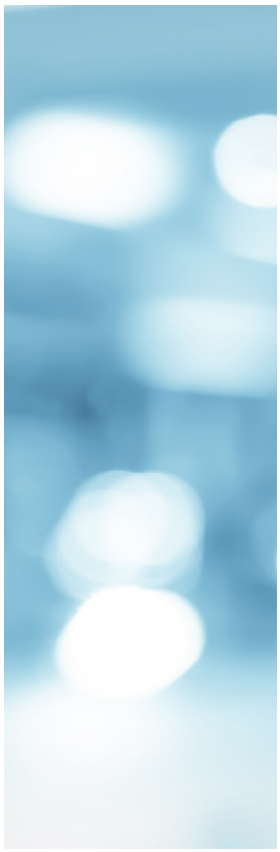
Patients and caregivers discussed several other important aspects of Strensiq which include:



- **Potentially serious reactions:** Cannon, a 17-year-old with HPP, describes a reaction that he and several others with HPP have experienced: “I’ve had episodes where I did my shots and I suddenly had a feeling like my throat was closing and I couldn't breathe. I thought I was dying. I had chills and the shakes for 30 minutes after my injection and never really found out why that happened. It happened again over a year later and it was really scary. I have talked to other patients who had the same thing and it scares me that no one really understands how or why that is happening.”

- **Unknown long-term consequences of high ALP levels:** Many patients and caregivers are eager for more research and information about the effects of long-term, elevated levels of alkaline phosphatase. Jennifer, who lives with HPP, said: ”I hope someone figures out what the excess amount of ALP causes in our bodies due to treating with Strensiq as such high numbers are concerning.” Kate, mother to a teen with HPP, noted that normal alkaline phosphatase for someone without HPP is in the 100-150 range but bloodwork for her daughter often comes back in the 7,000 range. Studies have shown that Strensiq can interfere with other laboratory tests due to the use of ALP- conjugated test systems. This can lead to inaccurate test results for certain hormones, bacterial antigens and antibodies. Unfortunately, many healthcare providers are unaware of this possible consequence and may not take into account the impact of enzyme replacement therapy when viewing test results.

- **Cumbersome temperature requirements:** Strensiq requires storage in the refrigerator, which can be inconvenient and stressful during school, work, and travel. Some participants talked about how they avoid traveling altogether. As Lara said: “It is very difficult to travel with Strensiq and we travel a lot for our livelihood.”



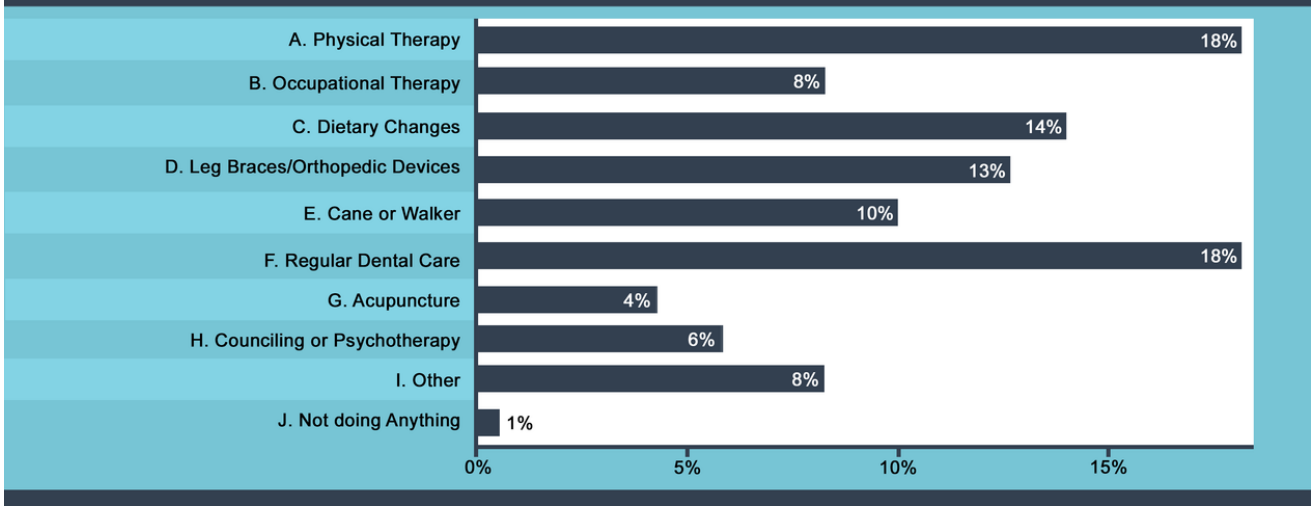
Other Drug Therapies

Although the conversation around treatments centered around Strensiq, several panelists briefly noted other pharmaceutical medicines used by patients for their HPP and related symptoms or comorbidities. These included Forteo (teriparatide), meloxicam, Plaquenil (hydroxychloroquine), gabapentin, Cymbalta (duloxetine), Tymlos (abaloparatide), steroids, and Fosamax (alendronic acid).

Approaches Beyond Medical Treatment

Besides medication treatments, many patients and caregivers talked about turning to other approaches to manage HPP symptoms. Physical therapy was the most popular approach, beyond medication, according to our poll (Appendix 5, Question 2). Caregivers also talked about seeing benefits from physical therapy in their children, starting it from a young age. An interesting aspect of physical activity that was reported by several people was efforts to maintain a delicate balance of staying active without overexertion.

Besides medications and treatments, what have you or a loved one used to help manage the symptoms of Hypophosphatasia? Select ALL that apply



Amy talked about the importance of physical therapy for her young daughter: “Due to the many factors hindering Aubrey's gross motor skills, we spend the most time focused on physical therapy.” While Cannon a 17-year old with HPP who was diagnosed at 18 months old said that he’s been in physical therapy for his whole life. Morgan, 17, also began physical therapy early on.

Pat, who lives with HPP, said: “Physical therapy, occupational therapy has been tremendously helpful” but did caution: “If I do too much exercise, then I'm extremely fatigued and it has a negative effect.” This sentiment was also echoed by Wendy, who lives with HPP: “It's that delicate balance of what is my body going to let me do…. if I push myself too hard trying to build endurance, now I'm going to fatigue and have a setback. It's an amazing balancing act.”

Additional approaches were highlighted throughout the discussions including regular dental care, dietary changes, orthopedic or mobility devices, occupational therapy, massage therapy, chiropractic care, oxygen therapy, meditation, aquatic therapy, naturopathy and others.

Hopes and Expectations for Future Treatments

While current treatments can help some HPP symptoms, there is a critical need for new therapies that can fundamentally change the course of the disease. Short of a cure, polling respondents overwhelmingly want an HPP treatment that will slow or stop disease progression (Appendix 5, Question 5).

Desired attributes of an ideal HPP treatment*
• Slows or stops disease progression
• Reduces pain
• Easier administration (less frequent or no injections at all; ideally pill form)
• Few or no side effects
• Help with brain fog

* Topics that received > 9% responses from polling participants and discussion points from audience participation.

Other top desired attributes from poll responses include reducing pain and having fewer side effects. This mirrored the subsequent discussions from patients and caregivers, who provided more context around the importance of these attributes for a potential new treatment.

- **Slow or stop disease progression:** Patients and caregivers spoke about the fear of the unknown as the disease continues to progress and what that means for their future. They reinforced the critical need for a treatment that can address the underlying disease itself.
- **Reduce pain:** Given the extreme and unrelenting pain faced by patients, many wanted a new treatment that can alleviate the burdensome pain. As one mother to a young child with HPP said, “I hope one day she can have even just a single full day of being pain free.”
- **Fewer side effects:** Patients need a treatment that not only works to alleviate HPP symptoms, but one that is tolerable.
- **Easier administration:** Many patients emphasized the serious physical and emotional damage caused by current injections. As Jennifer, who has a young son with HPP, wrote: “We would absolutely love a different option for a route of medication--anything other than injections.” Others shared that the desired administration for a future treatment would be a pill, patch, a less painful needle or less frequent injections, or IV. Ideally, a new treatment would not have temperature storage requirements.

When I think about Aubrey's future, knowing as of right now, her only option is daily painful injections for the rest of her life, it deeply saddens me. As other treatments become available, I can only hope that the treatment options have less of an impact on her everyday life, her mind, and her body

Amy shared her hopes for her young daughter with HPP

Benefit-risk assessment is the foundation for FDA's regulatory review of human drugs and biologics. The Benefit-Risk Framework provides an important context for drug regulatory decision-making and includes valuable information for weighing the specific benefits and risks of a particular medical product under review.

The chart below is based on input from the HPP EL-PFDD meeting held on November 15, 2022, including discussion during the meeting, polling data, and submitted written comments. This sample framework may help inform the FDA's Benefit-Risk Assessment for new HPP treatments.

	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	**Hypophosphatasia (HPP) is far more than "a bone disease."** HPP is a rare, genetic and potentially life-threatening metabolic disorder. People with this condition have low levels of the enzyme alkaline phosphatase (ALP). Although often characterized by its impact on bones and teeth, HPP symptoms and severity can vary widely, including within families. Severe types of HPP can be fatal, leading to stillbirths or children not surviving past one year of age.	**Life with HPP is profoundly unpredictable.** HPP touches almost all foundational aspects of a patient's life, as well as that of the caregiver and family unit as a whole. Living with intense, unpredictable symptoms can cause serious mental health conditions including depression, anxiety and in some cases, thoughts of suicide.
	Patients often experience intense, debilitating pain, often going to great lengths to adapt or adjust their lifestyle to cope. Many also face mobility issues, brain fog and fatigue, frequent broken bones, dental issues and serious mental health conditions.	**Patients and caregivers report fear, anxiety, and stress due to the unpredictable nature of symptoms, from one day to the next and as the disease progresses over time.** Patients worry about intensifying pain, disability and profound mental health impacts, as well as becoming a burden to loved ones. Parents live in fear for what their children with HPP will face in the future.
	HPP can impact all fundamental aspects of daily life. HPP can severely hinder a patient's abilities to sleep, socialize, exercise and maintain a career or go to school.	

	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	**There is one currently FDA-approved treatment for HPP which has significant challenges.** Enzyme replacement treatment can improve some symptoms but comes at the cost of painful injections (up to 6X/week). These injections can cause skin scarring, discoloration and lipodystrophy. Patients taking the treatment for years noted they are "running out" of sites. There are questions around the efficacy of the treatment when injected into sites where patients have lipodystrophy. Parents may need to physically restrain children to inject, with some developing an intense fear of the medicine. The treatment can also cause serious reactions, requires inconvenient temperature storage, and little is known about long-term elevated enzyme levels.	**There is an urgent need for a disease-modifying treatment that can stop or slow progression of HPP.** Currently no treatments alleviate most HPP symptoms or impact the trajectory of disease progression. **Patients with HPP and caregivers are desperate for a treatment that doesn't involve nearly daily, painful injections.** Long-term injections, which can cause physical and emotional damage, are not readily sustainable for many patients.

Conclusion

The November 15, 2022 HPP EL-PFDD meeting provided an opportunity for the FDA and other stakeholders to hear directly from the HPP community. Patients living with HPP as well as caregivers and parents of individuals with HPP described the disease manifestations and experiences, the impacts on their activities and daily lives, and worries related to life with HPP. They described various medications and therapeutic approaches and their perceptions about the efficacy of these treatments. They shared frustration with current approaches which fall short of alleviating most disease symptoms. The currently approved enzyme replacement therapy has many benefits along with many shortcomings, including frequent painful injections and other potentially serious side effects. HPP affects almost every aspect of a patient's daily lives and the family unit as a whole.

The participants at this EL-PFDD demonstrated that short of a cure, slowing or stopping the progression of HPP is a top priority for a future therapeutic, as well as more effective pain reduction. There is a critical need for easier medication administration for patients who currently endure multiple, painful injections each week which can cause severe physical and emotional distress.

Soft Bones is grateful for this opportunity to share HPP experiences through the EL-PFDD meeting and this Voice of the Patient report. We are continually inspired by the strength and resilience within the HPP community and hope the powerful insights shared will help spur innovation in a disease area desperate for well-tolerated, disease-modifying treatments.

Soft Bones EL-PFDD Agenda

Meeting Date: November 15, 2022

Time	Topic	Presenter
10:00 – 10:05 AM	Welcome and Opening Remarks	Deborah Fowler, President and Founder, Soft Bones, Inc.
10:15 – 10:30 AM	FDA Remarks — The Role of Patients in Drug Development	Patricia Beaston, MD, Office of Tissues and Advanced Therapies, CBER, FDA
10:15 – 10:30 AM	Clinical Overview of Hypophosphatasia	Michael P. Whyte, MD, Washington University School of Medicine, Shriners Hospitals for Children – St. Louis, MO
10:30 – 10:35 AM	Overview of Discussion Format	James Valentine, JD, MHS, Meeting Moderator
10:35 – 10:40 AM	Demographic Polling	James Valentine, JD, MHS, Meeting Moderator
	Introduction to Session 1: Symptoms & Daily Impacts	James Valentine, JD, MHS, Meeting Moderator
Morning Session: Living with Hypophosphatasia – Symptoms and Daily Impact		
10:40 – 11:05 AM	Patient Testimonials (Session 1)	
11:05 – 12:30 AM	Moderated Audience Discussion and Polling	
12:30 – 1:00 PM	Break	
Afternoon Session: Current and Future Approaches to Treatment in Hypophosphatasia		
1:00 – 1:05 PM	Introduction to Session 2: Current and Future Approaches to Treatment in Hypophosphatasia	James Valentine, JD, MHS, Meeting Moderator
1:05 – 1:30 PM	Patient Testimonials (Session 2)	
1:30 – 2:45 PM	Audience Discussion and Remote Polling on Topic 2	
2:45 – 2:55 PM	Meeting Summary	Larry Bauer, RN, MA, Hyman, Phelps, & McNamara, P.C.
2:55 – 3:00 PM	Next Steps and Closing Remarks	Deborah Fowler, President and Founder, Soft Bones, Inc.

TOPIC 1: Living with Hypophosphatasia – Symptoms and Daily Impact

1. Of all the symptoms and health effects of hypophosphatasia, which 1-3 symptoms have the most significant impact on you or your loved one's life?

2. How does hypophosphatasia affect you or your loved one on best and on worst days?

3. How has your loved one's ability to cope with the symptoms changed over time?

4. Are there specific activities that are important that you or your loved one cannot do at all or as fully as you would like because of hypophosphatasia?

5. What do you fear the most as you or your loved one gets older? What worries you most about you or your loved one's condition?

TOPIC 2: Current and Future Approaches to Treatment in Hypophosphatasia

1. What are you currently doing to manage your or your loved one's hypophosphatasia symptoms?

2. How well do these treatments treat the most significant symptoms and health effects of hypophosphatasia?

3. What are the most significant downsides to your or your loved one's current treatments and how do they affect daily life?

4. Short of a complete cure, what specific things would you look for in an ideal treatment for hypophosphatasia? What factors would be important in deciding to use a new treatment?

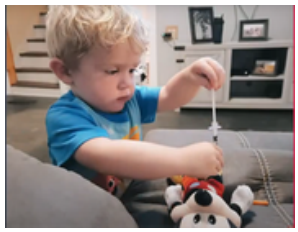
Topic 1 Panelists: Living with Hypophosphatasia — Symptoms and Daily Impact

Laiken's Story (mother to two young children with HPP)

My name is Laiken and I am the mother/caregiver of Rowan and Rhys, ages two years old and nine months old, who both are diagnosed with hypophosphatasia.

Both Rowan and Rhys were diagnosed prenatally. I was referred to Maternal Fetal Medicine, a high-risk specialist, for both of the boys pregnancies. Both boys were diagnosed with HPP via amniocentesis confirmation; Rowan at 24 weeks gestation and Rhys at 23 weeks gestation. Rhys' physical presentation has been less severe than Rowan's across the lifespan; Rhys is primarily affected in his lower arms/forearms, showing mild shortening and curvature, whereas Rowan is affected in all of his long bones with moderate shortening and curvature.

Despite medication therapy working to promote bone growth/strengthening, both boys remain in the less than one and less than 15th percentile for height. Shortening and curvature of the long bones was the first symptom of HPP that was detected. Other comorbidities of HPP that both boys have experienced include Vitamin D deficiency and hypercalcemia. Both boys have experienced growth, mineralization, and gradual straightening of their long bones (as evidenced by x-ray); this is entirely because of their current medication regimen. Rowan received occupational therapy up until he turned one years old; through OT we discovered mild deficit in the flexion of his left foot/ankle. Through continual exercises and stretching, along with weight bearing activities and use of KT tape, this has improved.



The most prominent symptoms or effects of HPP on not only the boys, but the entire family unit, has been fear and anxiety. Fear related to the unknowns of the diagnosis have been instilled in our family since before we received their diagnosis. I can recall the countless nights spent crying, yearning to find more information on this diagnosis, mourning what felt like the loss of a "normal" pregnancy and life for my children.

Every prenatal appointment, NICU round, and specialist appointment concluded with the reminder of what complications to monitor for; always reinforcing the idea that our boys condition wasn't stable and risked decompensation. This fear was instilled so deep that despite being told how stable Rhys' condition was upon discharge from the hospital that I called 911 his first night home because he suddenly wasn't acting his normal self and I mistook it for respiratory distress; I have never feared for my child's life like I did that night. I fear how my boys, affected with a rare metabolic disease with known height deficits, will be treated by a society that doesn't support being a "short boy." Will they harbor jealousies against each other as their presentation is so different despite being affected by the same disease? Will they ever find a supportive partner who they can have children with despite knowingly passing a genetically inherited condition? Both boys risk being affected by the constraints of societies social norms. At present day, we can see anxiety in the boys, created by medication administration. Fear of the pain of administration.

Hypophosphatasia continues to affect both boys physically at this current time with the potential to affect them socially as they grow older. Due to the nature of the diagnosis and not knowing how well their bones may handle contact/impact sports, we try to promote more individual or non-contact leisure activities – this is to prevent any additional risk of fracture. Rowan and Rhys are at an increased risk of being affected psychosocially; their diagnosis sets them apart from the "norms" of other children their age. Regarding infant handling, both children were handled with more caution specifically when being picked up and when having their diaper changed.

What I fear most as my children get older is the potential for them to decompensate; this can include losing their level of mobility to some degree and acquiring chronic bone pain. I also fear the effects of the diagnosis on their social development and mental/emotional health. What frustrates me most about the diagnosis of hypophosphatasia is the constant state of unknowns that the diagnosis carries, especially because every individual is affected differently in regard to level of severity, even if within the same family composition. Both boys were discharged from the hospital with many specialist follow-ups; every specialist educated us on the common comorbidities to watch for, reinforcing the fear that our children's now stable condition was not guaranteed.

The fear that was instilled in us, as parents, created a lasting anxiety that ultimately resulted in feelings of extreme isolation. While medication therapy has significantly improved the health outcomes of both children, the course of the disease is still unknown. We will not know if the boys will be affected with fractures, gait impairment, or chronic pain as they grow older. Not knowing the capacity in which my children may suffer is the hardest part.

Becky's Story (mother to child with HPP)

This story starts in a small village in China. A chubby cheeked baby girl with curved and twisted arms and legs was found on an old man's doorstep. My name is Rebecca and I am that baby girl's mother. My husband, oldest daughter and I got to wrap our arms around Juliana when she was 20 months old. She was full of light, mischief, determination, and was riddled with pain. She could not stand and her perfect little feet were twisted almost backwards. She was diagnosed with hypophosphatasia within a month of arriving in the United States. She didn't qualify for the Strensiq drug trial because we couldn't prove she was symptomatic before she was 6 months old. So, we spent our days treating her migraines, her back and neck pain, her constant vomiting and trying to keep up with her untamable spirit.

In spite of her pain and in spite of her inability to stand or walk, she climbed everything and developed her own sign language to communicate with us until she started using English words. We educated her preschool on the condition so they wouldn't send her home every time she threw up or be shocked when her teeth fell out roots and all. They made sure all vegetables were cooked soft for her toothless self and learned how to work the 5-pound twister cables she wore when they changed her diapers. Juliana was 3 ½ when she started Strensiq. She received three slow injections a week. Within a month she was able to jump and run. Her muscles grew stronger and she spent the entire summer working on riding a tricycle all the way around the sidewalk loop at preschool. When she finally completed the loop, her teacher cried when she told me about it. With treatment of Strensiq, her migraines went away, she stopped throwing up and her pain levels decreased.

When she entered elementary school, she was socially ready but we knew she would struggle academically. We had a hunch that she had some learning disabilities, which we had heard anecdotally could be connected to HPP. She has speech delays, ADHD, dyslexia, dyscalculia, working memory issues, and expressive language disorder. She repeated kindergarten and receives help from the special education team at school.

She works so hard to catch up in school. She is wicked smart, so determined, and loves homework. However, there are too many days when she comes home from school crying because she feels dumb. We work tirelessly to help her feel confident in her abilities and know beyond a shadow of a doubt that she is not dumb.
She receives dexmethylphenidate for ADHD and it works beautifully to help her focus in school and take her time on tests. She used to race through tests with very low scores, and now she takes about 3 times the length of her classmates and her test scores have skyrocketed.

She is now entering 4th grade. She has lots of friends who all know about her condition and slow themselves down to play with her at recess. She can't keep up with them, so they keep up with her instead. When she was recovering from a double tibial osteotomy in 2nd grade, there was a little boy who brought her a gift so that she could play in her wheelchair at recess with it. When she started walking with twin walking boots, there were a couple of kids who just sat on the swings with her or brought out sidewalk chalk to do with her. She sits out field day every year but helps her teacher take pictures. In PE, she requires a lot of breaks, but her PE teacher gets it and finds other ways for her to participate like score keeping or calling players out.

Outside of school, she loves horses and takes lessons from an adaptive teacher. Juliana is a natural on a horse. She is very frustrated that she can't play soccer or lacrosse like her friends because one accidental kick to the leg would break her. She tried ballet, but couldn't get her feet correct, but loves tap and Chinese dance. Juliana also suffers from medical post-traumatic stress disorder (PTSD). Sometimes it rears its ugly head after a painful injection or a doctor visit, and it's always present before and after a surgery. She has had six surgeries and two of them were two night hospital stays with a lot of pain and vomiting. We can always see a PTSD rage coming when she starts quietly and systematically tearing her room apart. I have learned that the best thing to do is stay close and when she is ready just wrap her in my arms and let her cry it out. She has told me repeatedly "Mom, I don't think I will reach my grown-up-hood." That's my biggest fear too.

Ellen's Story (HPP patient and caregiver)

My name is Ellen and my story is one of both caregiver and now patient. I was 4 years old when my sister was born with HPP. She had failure to thrive and at one year old her weight was the same as her birth weight. She did survive and my caregiver journey had begun, unbeknownst to me. Looking back HPP dictated our family life in every way.

Her first fracture that I remember was at age 3 and while sitting on the back porch eating corn on the cob. She dropped hers and reached for it from the bottom step. She tumbled from that one stair and broke her leg. That meant hospitalization, she would be in traction for three months.

After three months her break was never healed, so then she came home in a body cast (around her trunk and down to the toes on her broken leg). This meant bed pans, sponge baths and EVERYTHING brought to her. Weeks or months later when she finally got the cast off, her muscles were atrophied and then physical therapy started. When she finally got to the point of walking, it would take almost a year. Not long after, she would break again and it would start all over again and again and again!

They had re-diagnosed her with osteogenesis imperfecta and started rodding all of her long bones. That gave her much more stability. We all benefited from that because casts were not needed with these surgeries.

As an adult, I have always lived close and able to help when needed. I would leave school and later work and go straight to the hospital to do my share with the evening shift to help feed and entertain during her numerous hospital stays. When I married, my husband was aware that she would live with us when necessary.

Fast forward to four years ago when her health started to fail. Her lung function is affected because of weak rib bones and she had to go on oxygen. HPP effects a lot more than just bones and she was really not doing well. We sold our house and built one that was handicap accessible that would fit my 93-year old parents, my sister, my husband and myself.

My sister has gone on treatment and it has turned her life around. She is off oxygen and her health is much better. Now if she cracks a bone it heals in a normal healing time and usually doesn't have to be hospitalized. It has taken her from wheelchair-bound to part-time crutches. It's not a cure and it doesn't fix everything but it certainly made everyday living much easier.

Mom, Dad and I were told we were carriers of HPP and would never have any symptoms. We now know that is a false statement and we are all in different phases of onset of HPP.

My parents have had major joint problems due to HPP. Dad had to have both knees and hips replaced. Mom's spinal scoliosis and collapse caused her to need a walker long before her aging should have needed it. She also needed both shoulders replaced due to unexplained bone deterioration. Since there is a wide range of symptoms presenting with multiple intensities within family members with the same HPP genes, it's difficult to define HPP. This leads to missed diagnosis and diagnosis with unexplained findings.

I am dealing with pain in the neck, hips, ankles, back and feet. I am a medical assistant and am on my feet all day and some days the foot pain is so bad I can hardly walk the halls to do my job. It can stay for days to weeks and then again it can last for only hours. My neck pain is worsening with computer work and then triggers migraines. I need to continue working. I'm not able to retire early, so I just push through.

The bone/muscle/calcium crystals that cause the pain is disabling at times. Since it can be gone in hours to days, it's hard to get doctors and employers to believe you aren't making it up. I get home and make dinner and help clean up. I am physically and mentally exhausted when I finally land on the couch. I can barely get up and keep moving when it's time to get everybody ready for bed.

With every pain comes the panic of thinking- is this the day I become disabled and then what? Thank you

Sherri and Maya's Story (mother and daughter with HPP)

Sherri:
Hi, my name is Sherri, and I live in Cincinnati, Ohio with my husband, Mike, and my daughter, Maya. I also have a daughter, Syreeta, who lives in Cleveland.

In 2019, Maya and I were diagnosed with hypophosphatasia (HPP). Maya was 15 and I was 55. Maya and I share the same genetic mutation but our symptoms vary greatly. Syreeta was diagnosed one year later without genetic testing due to low ALP, high B6.

When Maya was 11 her health seemed to decline rapidly. She went from constantly running around the backyard to sleeping all the time and complaining about pain. She fell asleep during class, and she cried every day that she hurt. This started our 4-year journey to a diagnosis of HPP.

Within 4 years we saw over 11 specialists, received 21 diagnoses and we were prescribed 32 medications. None of which took away her pain and fatigue. By the end of 6th grade, she was a shell of the child she used to be. My heart was broken and she didn't want to live the life she had. She rarely left her room and when she did my husband had to carry her due to the pain she had in her legs.

Although all three of us have HPP, our symptoms vary greatly. Syreeta is 23 and has been able to attend college, get her degree, and start a job. I have worked professionally and raised a family. We both struggle daily with our health from chronic conditions to autoimmune diseases.

Maya:
Hi, my name is Maya, I am 18 years old, and my life has been terribly altered because of hypophosphatasia.

In 2019, I was diagnosed with HPP. For many years, I had very bad pain and fatigue. I suffer from many chronic illnesses including autoimmune disease.

I played sports as a kid. I was good at gymnastics, tumbling and cheerleading. I enjoyed diving, volleyball, soccer and lacrosse. I did get injured playing these sports I just didn't know I had HPP.

Summer of 5th grade changed for me. I went to summer camp for the first time for 2 weeks, afterwards I felt sick and spent a lot of that vacation in bed. The rest of that summer I was very tired and sick.

I was excited to start the first day of 6th grade. But my body was hurting so much and my head felt like it was exploding. I finished the day in tears. I went straight to my mom's car and said take me to the hospital because something is very wrong with my body.

They gave me a migraine cocktail and ran some tests. They assured me the tests were fine and that I was fine. I struggled every day to either go to school or to stay at school. I was falling asleep in class. The fatigue I felt was so overwhelming. The migraines were awful and I couldn't even keep my eyes open. The lights hurt my head so much. It was hard because I know my teachers didn't understand and I don't think they believed me. I tried to tell them how much my body hurt and/or how much my stomach hurt but I looked normal to them. I started having seizures that were staring spells. I was missing school trying to find out what was wrong.

My classmates told me I was faking and this turned into bullying me. I was struggling with my mental health. Eventually, I couldn't attend school. I was too sick. In the years to follow, we tried many different methods for education but it was very difficult. I couldn't keep up, I couldn't concentrate. I could only think about the pain I was in.

I had so many doctor's appointments and nobody could tell me what was wrong with me. Some doctors even said it was in my head. I was taking so many pills but none of them were making me feel better. Some of them actually made me feel worse. I just felt like nobody understood what I was feeling. My mental health continued to get worse, and I felt totally isolated.

My new school was great and put many precautions in place to help keep me safe. But it was hard for me to be in that kind of environment because of my anxiety. I still missed a lot of school for many reasons but the school still supported me.

I'm mostly homebound. I'm trying to get out more but it's challenging to find friends and not feel so anxious. I've been totally isolated from having HPP that friendships have been impossible to have and maintain.
I've had countless bone fractures and injuries. I have a fear that I won't be independent when I want to be independent.

I'm 18, and I worry about college, working, getting married, and having kids.

I JUST WANT TO FEEL BETTER.
I want to laugh again like I did when I was a little girl.

Amy and Suzanne' Story (HPP patients)

(Suzy) My name is Suzanne. I have always dreamed of flying, in a body with wings, agile, graceful and without pain.

(Amy) Hello, I'm Amy, Suzanne's identical twin. As a child I saw a man with a prosthetic leg. Ever since, I've dreamed of having them. How great it seemed it would be to have legs that don't hurt!

(Suzy) After a lifetime of symptoms and searching a genetic test showed we had an ALPL gene mutation known for causing HPP. But even still, doctors didn't believe us.

One doctor told Amy she couldn't have HPP because she didn't die as an infant. Another said she couldn't have HPP because she could get up out of a chair. Another said our gene mutation did not cause disease.

(Amy) As an infant I did spend a month in the hospital. The doctors wouldn't let my mother visit because I cried too much. They told her to go home and focus on the baby that was going to live. Years later, my own daughter cried for her first 18 months. We went to countless doctors. Year after year we were told, "she just has a low pain tolerance," "she's faking," "she just wants attention."

(Suzy) Our mother had been shamed by so many doctors that when we were kids, she told us not to tell our doctors about our unusual symptoms. Our grandmother died never knowing why she couldn't walk well. We thought she just didn't try hard enough. We didn't understand that all our symptoms were connected.

We had 'lazy eyes' which delayed our reading. Amy had 13 years of speech therapy. We've had terrible "growing pains" which we never outgrew. Sometimes, all of my teeth were loose. We had dysautonomia but we wouldn't learn what that was until we were 52 years old. Some of the symptoms or comorbidities of HPP are strange and under diagnosed diseases in themselves. The overwhelming variety of symptoms and lack of understanding can make you feel crazy. Depression and anxiety added extra layers to an already difficult diagnosis journey.

(Amy) We have had surgeries to correct our eye muscles, knees, wrists, and torn rotator cuffs. We've had bursitis, terrible tendonitis in our arms and ankles, frozen shoulders, plantar fasciitis. We have calcium deposits that shred tendons and destroyed cartilage. We've had broken wrists, ribs, fingers, toes, and micro fractures in our feet. Our spines have scoliosis, with bulging disks, hernations and severe degeneration.

(Suzy) We have osteoporosis, early cataracts, lifelong tinnitus, insomnia, problems with balance and regulating temperature, sleep apnea, severe fatigue, muscle pain and weakness, and Chiari Malformation…. Amy suffered from lifelong constipation. Her migraines have been persistent and debilitating. The bones in our forearms are fused, limiting mobility. The worst of all the kinds of pain we experience is a kind of neuropathy which makes it feel like our legs are on fire.

(Amy) The thing about having undiagnosed HPP is that you end up getting all kinds of treatments, surgeries even, that don't help. Until you address the underlying cause (low alkaline phosphatase) you are just chasing symptoms, symptoms that lead in 1000 different directions.

My body was in so much pain, even while sleeping, that I'd wake up crying. I was disappointed to wake up every morning, not knowing how I could get through another day.

(Suzy) As kids we were slow and clumsy. We couldn't move fast. No one wanted us on their team. We thought we just needed to try harder, ashamed of anyone knowing how hard we were working to keep up.

My mind was slow, in a fog. I couldn't hold onto thoughts or find words. I couldn't remember. Homework took forever.

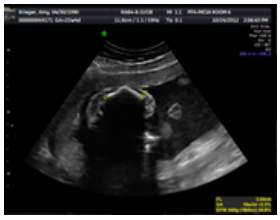
At age 50. a city bus grazed my hip while I crossed the street. I had never been so scared in my life but I was not able to move any faster. That's when I finally realized that I had been trying as hard as I could all along.

My fatigue, anxiety, pain and brain fog were so bad that I had to quit my job. Amy pushed forward for a diagnosis. Finally, at age 53, our diagnosis was confirmed!

(Amy) When I first learned that we had HPP, I wondered if the leading cause of death among HPP patients was suicide. The pain and lack of hope were unbearable. But now, because of all we've gone through, we know our children and grandchildren will be spared living undiagnosed.

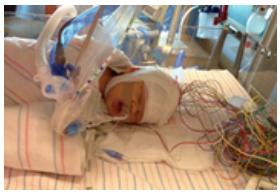
We are hopeful that they will have better treatment options. With a disease so varied in symptoms, even among identical twins, to have multiple treatment options will be huge in helping us to live our lives to the fullest.

Topic 2 Panelists: Current and Future Approaches to Treatment in Hypophosphatasia



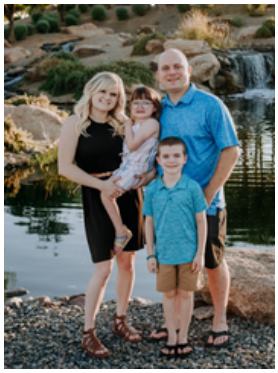
Amy's Story (mother to a child with HPP)

Imagine the excitement an expecting mother feels and the joy racing through her body as she sees her baby on the screen during an ultrasound. Then, suddenly feeling the emotion in the room change. Seeing the look of confusion and panic that is written all over the sonographers face. Now, the excitement and joy are quickly turned into sadness and worry. And that isn't even the worst of it. After what seems like an eternity, the doctor enters the room and tells the mother that if her baby lives past birth, the baby will die before they are even 1 years old. My name is Amy and this was my harsh reality just a mere 9 years ago.



I was a young mother never expecting to hear anything close to what I was told. I was expecting to hear if my husband and I were expecting a baby boy or baby girl and how big our baby was but what I was given was our unborn baby's death sentence. During the remaining weeks of my pregnancy, I sought multiple other opinions. I was given options ranging from if I chose to continue my pregnancy, I would be considered high risk and monitored closely all the way to recommending that I terminate the pregnancy. At that point, I was past 20 weeks and even if medically necessary, it was still illegal here in Arizona. Although I was given "choices" the only choice for me was to continue my pregnancy knowing the entire rest of my time growing my baby could potentially be the only time I would have with her.

Fast forward 9 years and I am lucky enough to be able to still kiss my daughter, Aubrey, goodnight and tuck her into bed. Treatment options were simple to navigate; because there were no treatment options. The days following Aubrey's birth, I knew something still just wasn't right. Aubrey began seizing daily, which added to the complexity of her hypophosphatasia diagnosis. She was very small considering she was born full term. In just the first few weeks of life, Aubrey had been hospitalized multiple times. Then, out of the blue, I received a phone call from Aubrey's neurologist informing me that he had come across a clinical trial for a possible treatment option for hypophosphatasia.



We jumped on the opportunity simply because with no treatment, Aubrey's prognosis was not very promising. Her bones were so fragile they could barely be seen on imaging. She was struggling to gain any weight. Aubrey was not hitting milestones as other infants her age. The clinical trial that saved Aubrey's life is what we now know as Strensiq.

I would do anything I had to do to ensure my child survives, but Strensiq is not a perfect solution. Aside from the obvious of having to administer an injection up to 6 times a week, the injections are painful. The frequency of the injections makes it difficult to rotate injection sites causing the sites to become very sore, bruised or red. Over time, this also caused lipodystrophy at the injection sites. Finding the right dose of Strensiq can also be difficult. Finding a doctor who feels comfortable prescribing Strensiq is one thing but knowing how to calculate the right dose is tedious. Many factors play into dosing such as body weight, blood work and imaging. Following up with ophthalmology and getting routine renal ultrasounds to monitor for potential calcium deposits from Strensiq can be time consuming as well as stressful. Even with Strensiq, it doesn't eliminate hypophosphatasia from showing its ugly face.

Aubrey has 2 genetic mutations and suffers from severe infantile hypophosphatasia. Aubrey still experiences bone fractures, failure to thrive, hypotonia, severely delayed gross motor abilities, tooth loss, hydrocephalus, severe central sleep apnea, and the list goes on. Aubrey has a multidisciplinary care team of over 13 specialists. Aubrey also attends multiple therapies throughout the week ranging from 1-3 hours. Aubrey receives physical therapy, occupational therapy and also feeding therapy. Due to the many factors hindering Aubrey's gross motor skills, we spend the most time focused on physical therapy. Aubrey has undergone 15 surgeries and countless in-office procedures. When I think about Aubrey's future, knowing as of right now her only option is daily, painful injections for the rest of her life, it deeply saddens me.

As other treatments become available, I can only hope that the treatment options have less of an impact on her everyday life, her mind and her body. I hope one day she can have even just a single full day of being pain free. Lastly, with me being a carrier of hypophosphatasia as well as my son, Maddox who is 8 years old, I fear if either of us need treatment at any point, what that would look like. I also worry that if I need treatment later in life, how that would impact my ability to be Aubrey's primary caregiver.

Debra's Story (older patient with HPP)

My name is Debra and I live in New York. I was diagnosed with HPP very late. I was in my 60s. I recall being told by our family doctor that I had "growing pains" as a 10 or 11-year old, nothing more.
Last September, I started Teriparatide, a generic version of Forteo, daily injections after a difficult 1 1/2 years on Strensiq. I was not able to move or get out of bed on my own during some of the initial time that I was on Strensiq. This situation did subside somewhat, but over the course of being on this medication, I would feel as if I was being pushed backwards when I walked. I would have to stop walking. I was extremely slow, as if I had aged decades. Now, on Teriparitide, I have regained some normalcy, though varied, in my level of activity. This medication is prescribed to treat severe bone loss. I was diagnosed very early with osteopenia before menopause and soon after diagnosed with osteoporosis. I have no idea if this particular medication is helping.

Originally, upon diagnosis of osteopenia, I was given Fosamax for over 7 years, increasing the dosage continually. It did nothing. I saw many doctors for fatigue and pain for years. I was told I was depressed, had fibromyalgia, an active toddler, etc., etc. Prior to Strensiq, I was given Prolia, a timed injection every 6 months to stimulate bone growth. Nothing. I lost 2" during those 2 years. Originally under 5' 2" every inch matters. That doctor and several others, specialists in this field of endocrinology and rheumatology, commented on my low alkaline phosphate but said to forget about it. They didn't know what it meant and didn't think it meant anything. Google would have been very helpful.

Last year, I had a joint replacement. After multiple years of pain, limited use and Physical Therapy, my arm literally got stuck in space. I couldn't move it. A large calcium deposit had grown around the shoulder joint to protect the area. It had to be removed. I have calcium deposits all over my body- from neck to feet, some visible, some felt when I lean against the back of a chair. I am told that this is the body's attempt to replenish bone- unfortunately these deposits are in the wrong places.

Besides bone on bone on the shoulder joint, this issue had to be addressed and surgery became essential. I stopped Strensiq in May of 2021 at the time of my surgery. Slowly, very slowly, I have regained some limited strength and am trying to add muscle to support my body. I continue to lose inches.

Exercise does help. I try to limit pain medication. I have used lidocaine patches, steroids and non-steroid drugs, ointments, acupuncture, massage, a chiropractor and other body work expertise as expense and level of pain allow and necessitate. I limit my activities unfortunately as a coping strategy.

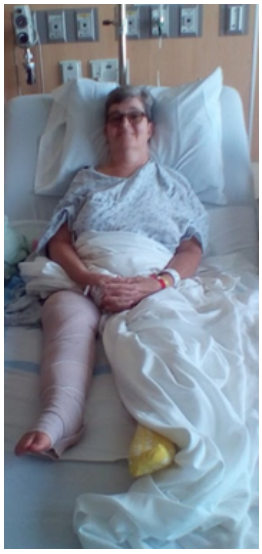
As I mentioned, I do not know if my current medication of daily Teriparatide is working. It has been almost 1 year. I must be on this drug for at least 2 years. This medication is for bone loss only. An upcoming DEXA test will hopefully show some result in the next month. I am told this drug works with HPP patients. I am also told that my particular mutation exists in three other patients in the country so far. My doctor mentioned this to me after a major endocrinology conference and consultation with another endocrinologist who is a specialist with HPP.
I do not know the other patients with my mutation nor are there any similarities in our background.

I continue to work. I am an artist and maintain my studio and practice. My ability to lift materials, bend and move in general, that with extensive fatigue, is challenging at best. I am not working, nor have I ever worked, at the capacity that I wish. Walking, stretching, moving, resting all help- that and focusing on other, more positive things. Pain and loss of mobility affect every day of my life and limit my activities. My level of activity does vary, but I have never felt that I was totally engaging in life as I wish- as if a life half lived.

Susan’s story (HPP patient)

I’m Susan, I was diagnosed with hypophosphatasia within 3 months of my birth in 1960. There was no treatment available for HPP. The specialist told my parents I wouldn’t live past my first birthday, and if I did I wouldn’t walk or talk. My known fracture happened at 6 months old while taking a nap, I tried to roll over like every 6 month old does and I broke both femurs. X-ray at that time showed I had 7 other fractures my parents nor doctors were aware of. Some they said happened in utero and during birth.

Since I was 3 years old and kept fracturing and having pneumonias the doctor thought they diagnosed me incorrectly. They changed my hypophosphatasia to osteogenesis imperfecta with unexplained low alkaline phosphatase. Since this was the next rare disease that fit close to my symptoms of low muscle tone and failure to thrive after birth.



With the new diagnoses there was a new procedure that could keep my long bones from displacing. It was a surgical procedure that placed an internal rod down the central of the long bones and do at least three osteotomies to straighten the deformities caused by rickets/osteomalacia. This surgical procedure took 4 to 6 hours, and then you were placed in a spica cast from your arm pits to your toes for 3 months. Once the bones healed, I then had 9 weeks of rehab to get me standing and then walking with crutches. It took a good 10 months before I was fully mobile again and by that time I would fracture or need a new type of rod to support the growth skeleton. These procedures happened about every 18 months to 24 months as the soft bones would pull away from the support of the rods. Because of this it made it difficult to maintain a job because of the amount of sick days I would need to take off. As I aged and degenerating part of HPP became more than just fractures, the joint and spine degeneration caused my health to deteriorate. I needed oxygen at night because my ribs were disappearing on X-rays making it hard to breath. My social and ability to work was impossible.

When I was 54 years old I was able to start taking Strensiq and those shots totally changed my life and every aspect of daily living. I went from fracturing 3 long bones a year to just small fractures that didn't need any surgical fix. Within the first 14 months on Strensiq my right humerus that was fractured and surgically fixed but became a non-union, healed solid. My arm was able to gain muscle tone as did all muscle. I didn't need to be on oxygen anymore as now all of my ribs are visible. During a plate removal my orthopedic commented that before Strensiq he could push a thin wooden tool through my bone with a figure pressure. But now he can't use a metal pick to penetrate my outer part of the bone. So even though I still get hairline cracks from time to time, my quality and independence of life is vastly improved.

As good as Strensiq is, there are many things of HPP it doesn't address. It helps the skeleton but it doesn't improve the joint deterioration nor joint swelling. Strensiq is also a temperature control drug so it makes traveling whether 2 days or 2 weeks a bit hard to plan. Making sure ice packs stay frozen enough to pass through TSA becomes very challenging.

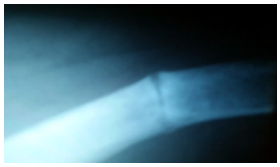
The one thing I would like to see changed, is the frequency of taking the injections. Six days a week is working for my body but is very inconvenient. I self-administer all my injections and have to make sure I have time in the evening to include these shots at least 2 hours prior to going to bed. I have rotated injections sites over my entire body for 7 years and it has left marks of lipodystrophy in all these areas. To that point, wearing summer clothing exposing arms and legs can cause me a lot of embarrassment.

Looking forward to the possibility to having a treatment that treats more of the symptoms of HPP because hypophosphatasia is more than loosing teeth when you are a toddler and fracturing throughout your life. The degeneration of joints and stenosis of the spine and skull are large concerns that lead to immobility that has not been addressed. I would hope one day that doctors would have a choices in treating HPP wide ranges of severity and symptoms. As we are all different and need choices of treatments to help as HPP changes throughout our lives.

Sally's Story (patient with HPP)

My name is Sally and I live in Texas with my husband, Alex, and my son Nick.
I was told as a young child that I was a very rare person! Indeed, I was, with only 1: 100,000 having HPP! I thought I was an only child until one day I was searching through my mom's dresser drawer and found a box containing the most darling leather Mexican baby shoes and my Mom broke down and told me for the first time ever that they had been my older sister's shoes and she died when very young in the early 1950's. She had HPP also but was diagnosed with Rickets and was given massive amounts of Vitamin D, which is what

ultimately led to her death before age 2. Patty was very, very fragile. As a child, I tried horseback riding to roller skating, etc. I was very adventuresome. I have had multiple fractures, that started in 1976 when in college, and then a car accident in 1982.



Since then, I can't even count the metatarsal, tibia, fibula, elbow, and shoulder fractures I have had. I tried one drug, but in the end, it did not change anything for the better. My doctor would get tears in his eyes because he could not comprehend how anyone could break so spontaneously. He hated to tell me we had more fractures to deal with at this visit, etc. An accident on an 8th Grade East Coast Historical Trip, threw my whole body into a fracture mode. It lasted for nearly 15 years.

Eventually I was placed on the newly approved Strensiq for Congenital Hypophosphatasia. Had I never been told about Strensiq I do think that I would have ended up in a long-term care hospital, since every bone was one by one breaking in my body. Dosing of 4 times a week with the Asfotase Alfa Enzyme (80 mg/0.8 mL) truly made the difference in my life. My endocrinologist that put me on Strensiq was videotaping me at each returning visit with me getting up and out of that wheelchair! I have never had one fracture since being put on Strensiq 5 years ago! which make a huge difference in the quality of life! The only "downside" of taking Strensiq for me is Lipodystrophy in my stomach, or an atrophy that was pretty severe of the stomach where injection sites were administered. In 10/2020 I had radical Lipodystrophy surgery of my stomach with Lipo and repositioning of the belly button, etc. My Plastic surgeon had me on some weight loss medication 6 months prior to the surgery date to be as close to my ideal weight as we could get. I ended up with a 70-pound weight loss. It has changed my life and also helps a lot with better walking abilities. Per my doctors, they want me for the rest of my life to be on both Topiramate 50 mg twice a day and Phentermine 37.5 mg (one tablet before breakfast). I take Blood Pressure medication only as needed now, which is rare. I take Losartan Potassium 50 mg. tablets. I take my BP twice a day. It is usually low!

I have HPP related hydrocephalus, and I know I have had it since I was little. I always thought that whooshing sound when I tied my laces up was normal! As an adult, however, the pressure and pain has intensified. I now take Fioricet which has Butalbital in it (50 mg) and Acetaminophen (325 mg) and Caffeine (40 mg). It does not get rid of the Hydrocephalus, but it takes the pain away.

The headaches arise every 6 hours, so I take 4 pills per day. No neurologist thinks shunting is something we should consider since both lateral ventricles are involved, and they are hard to access. I also have a Chiari I Malformation, but, at my age, neurosurgeons are not really wanting to operate.

I am in Physical Therapy, and I am getting my core back, gradually after all these years. I feel that massage therapy really helps with making those sore and tired muscles that ache non-stop just feel so much better. As long as everything is done gently, I am fine. Chiropractic care I am very cautious with, and I insist that everything is done extra gently and not by hand. I have been hurt by Chiropractic care many times.

Once in a while I wake up and I just know some gigantic mosquito nailed me during the night and then I remember this is where I gave myself an injection! It can once in a while turn into a large super itchy, patch of red. Some days it is so easy to give myself an injection, and other days it is like placing the needle into a brick wall.

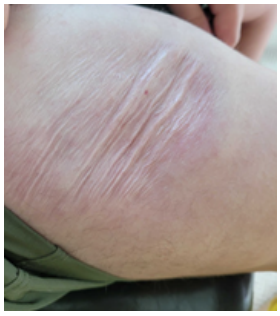
I totally would love some kind of oral medication instead of the needle injecting of Strensiq if that was ever possible. To take a pill or a powder would solve so many issues for so many of us! Gene therapies are in the works, and that would be fabulous also!

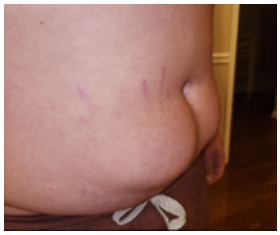
Cannon's Story (young patient with HPP)

Hello. My name is Cannon Sittig.
I was diagnosed with hypophosphatasia when I was 18 months old. As far back as I can remember, I've been dealing with HPP.

When I was young, I couldn't walk until I was 5. I remember wanting to walk in my school Halloween Parade, but they had to pull me in a wagon. We got creative though and made it work. I participated in the clinical trial for Strensiq when I was 4 years old and I am still on therapy today.

I've had bilateral knee and ankle surgeries to fix bone deformities in my legs. I've been in physical therapy my whole life. I have special orthotics that I am supposed to wear in my shoes, but I really can't stand them. I've also had two skull decompression surgeries to help me with my chiari malformation.





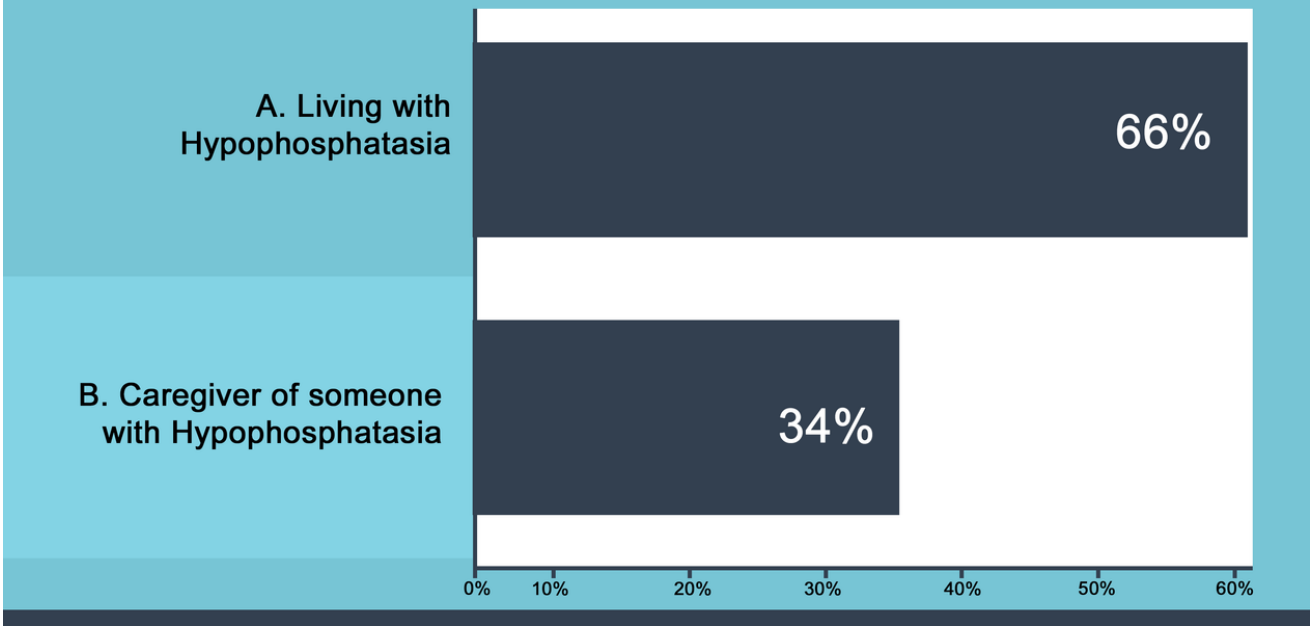
I can't walk for long distances or run because of pain in my legs. But the biggest challenge I have lately are my injection sites. Right now, I inject 5 times a week. It is a lot for me to handle because while I am so grateful for my medication since it has made me able to walk and have more stamina, I am even able to play golf with my high school golf team, I am running out of places to inject because of the scarring that I have from 13 years of shots. My doctor has advised me to stop injecting in my arms and stomach. The spots that I inject look purple and bruised. My stomach looks disfigured and looks abnormally swollen, and never goes away. I'm currently only able to inject on my thighs and my backside… and my doctor doesn't know how much longer my thighs will hold up.

I've also had an episodes where, when I did my shots, I suddenly had a feeling like my throat was closing and I couldn't breathe. I thought I was dying. I had chills and the shakes for 30 minutes after my injection and I never really found out why that happened. It happened again over a year later. It was really scary. I have talked to other patients who have had the same thing – and it scares me that no one really understands what is happening or why. No one can tell me how to prevent it from happening again in the future and now that I'm getting ready to go to college, I'm afraid of it happening when I'm on my own. Then what would I do?

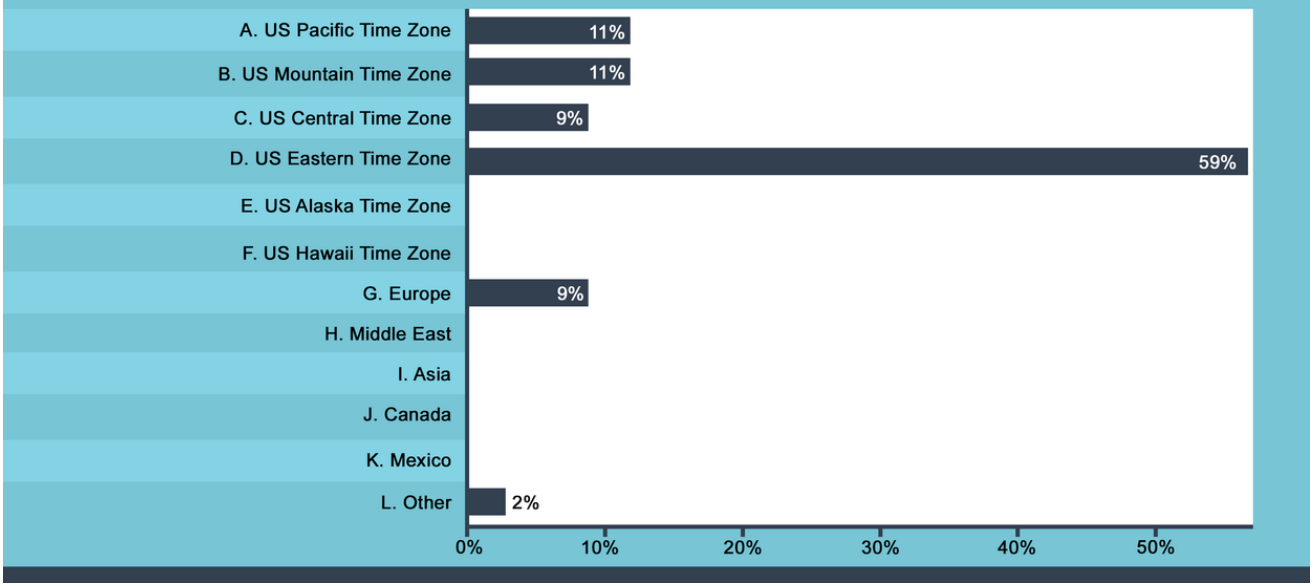
If I'm being honest, I'm worried about my future. I worry about having another reaction every time I inject. And then I worry that if I run out of place to inject my medication, how will I be able to continue walking or playing golf. I'm also worried about what will happen to my bones. I hope that researchers will not give up on HPP and my mom keeps telling me they are working on a cure. That is what keeps me going and gives me hope. Thank you for listening.

Results of Demographic Polling Questions

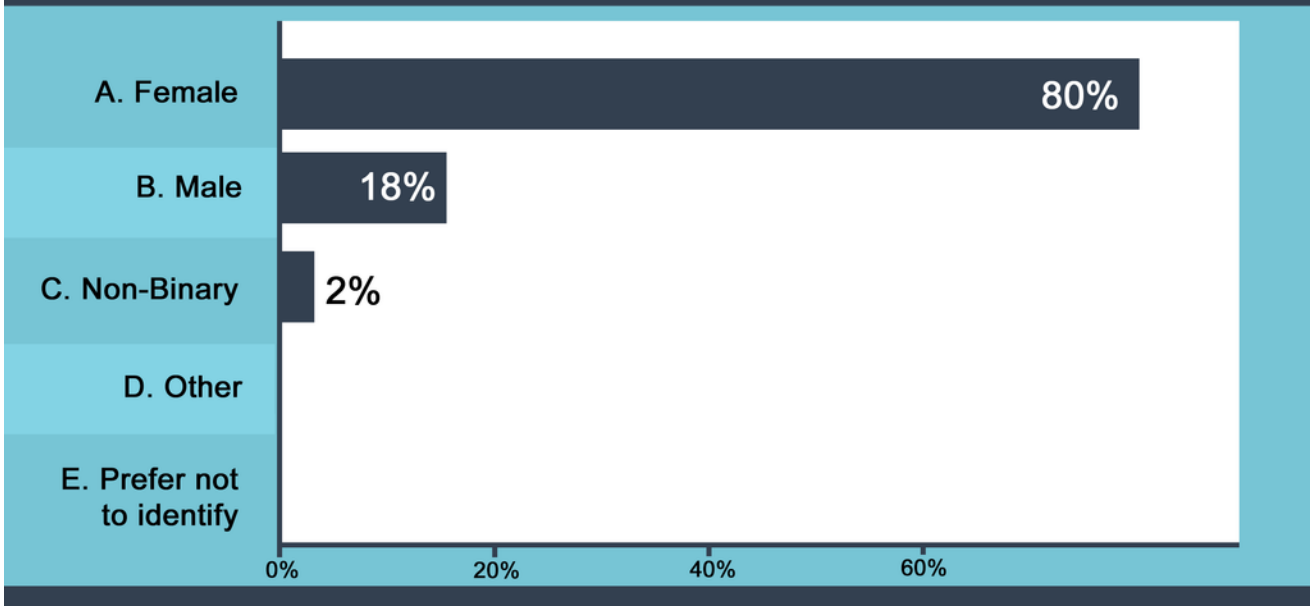
1. Are you:



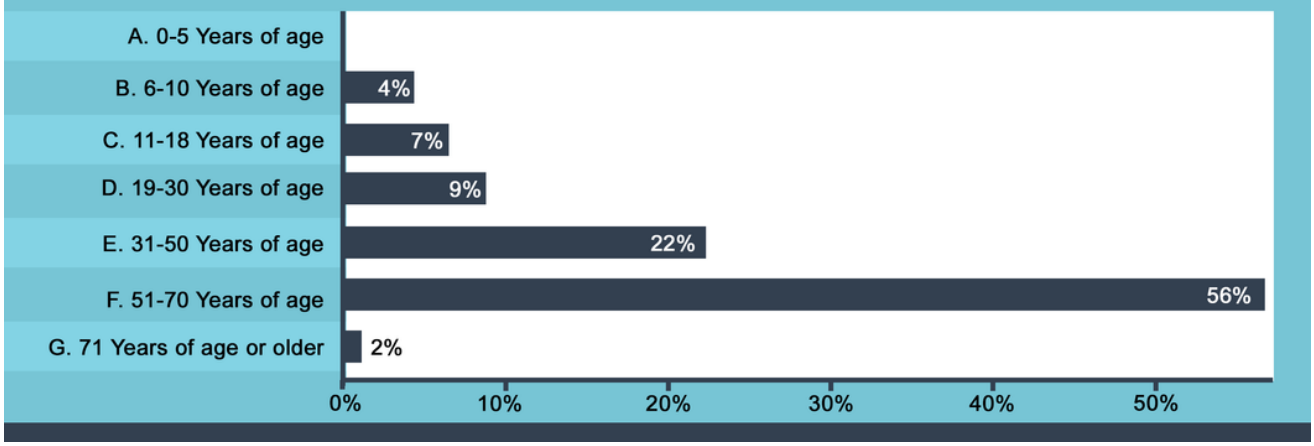
2. Where do you currently reside?



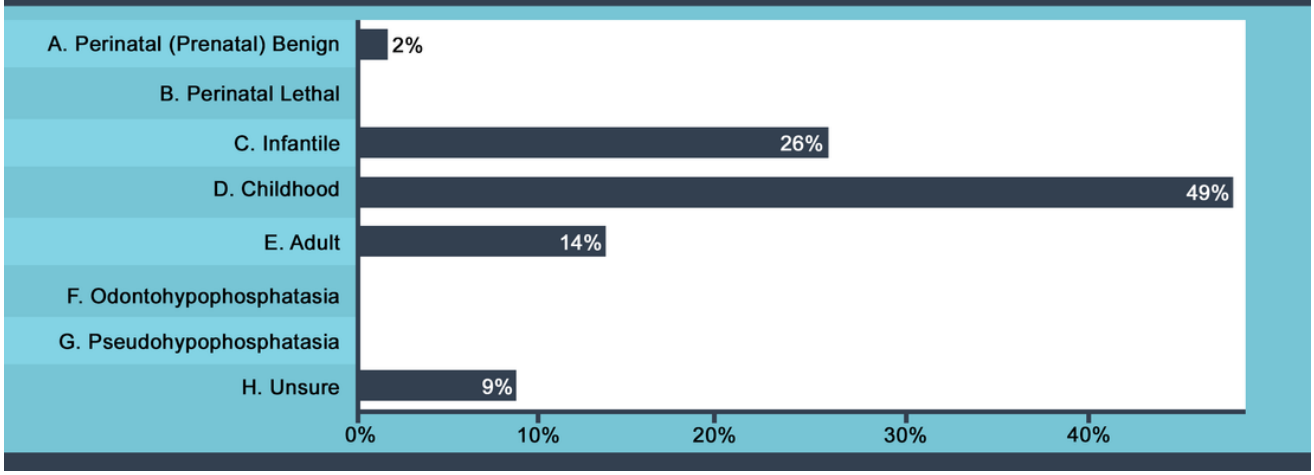
3. Are you or your loved one with hypophosphatasia:



4. How old are you or your loved one with hypophosphatasia?

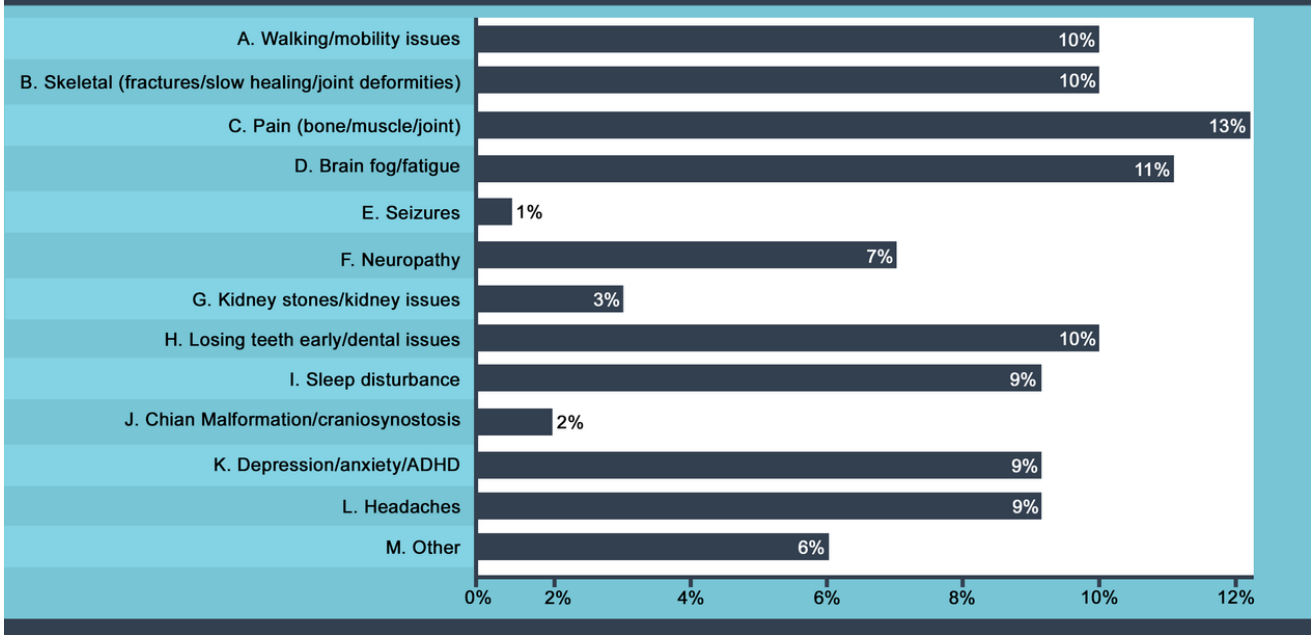


5. What type of hypophosphatasia do you or your loved one have?

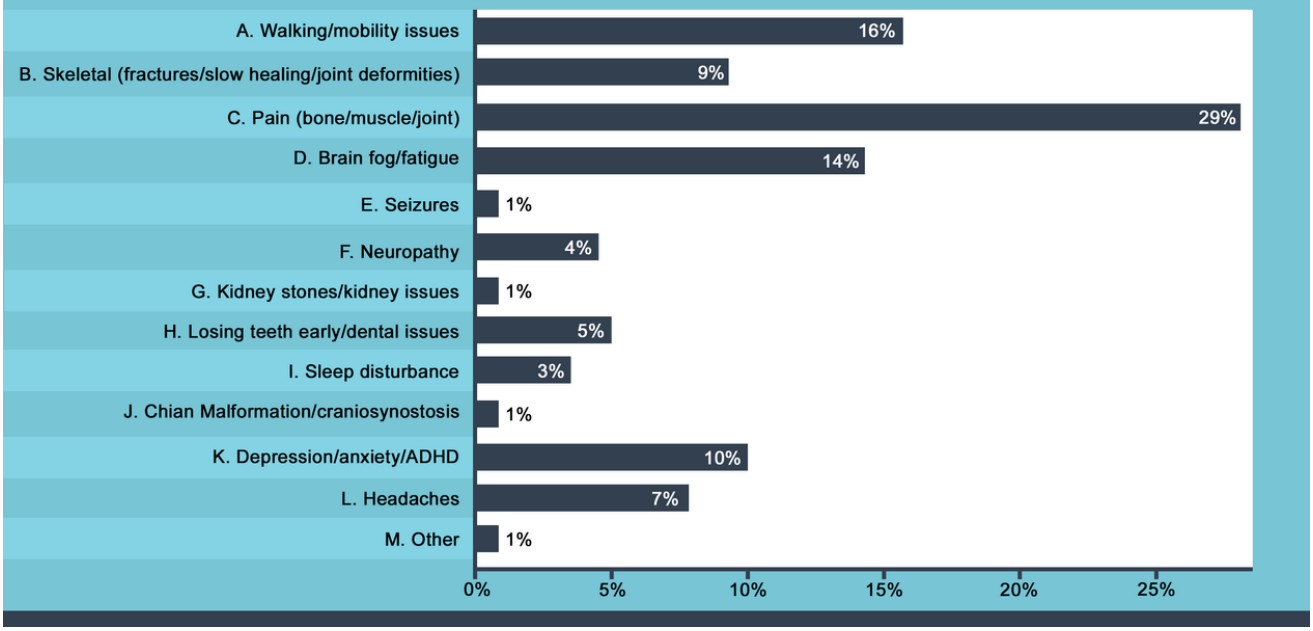


Topic 1 Polling Results

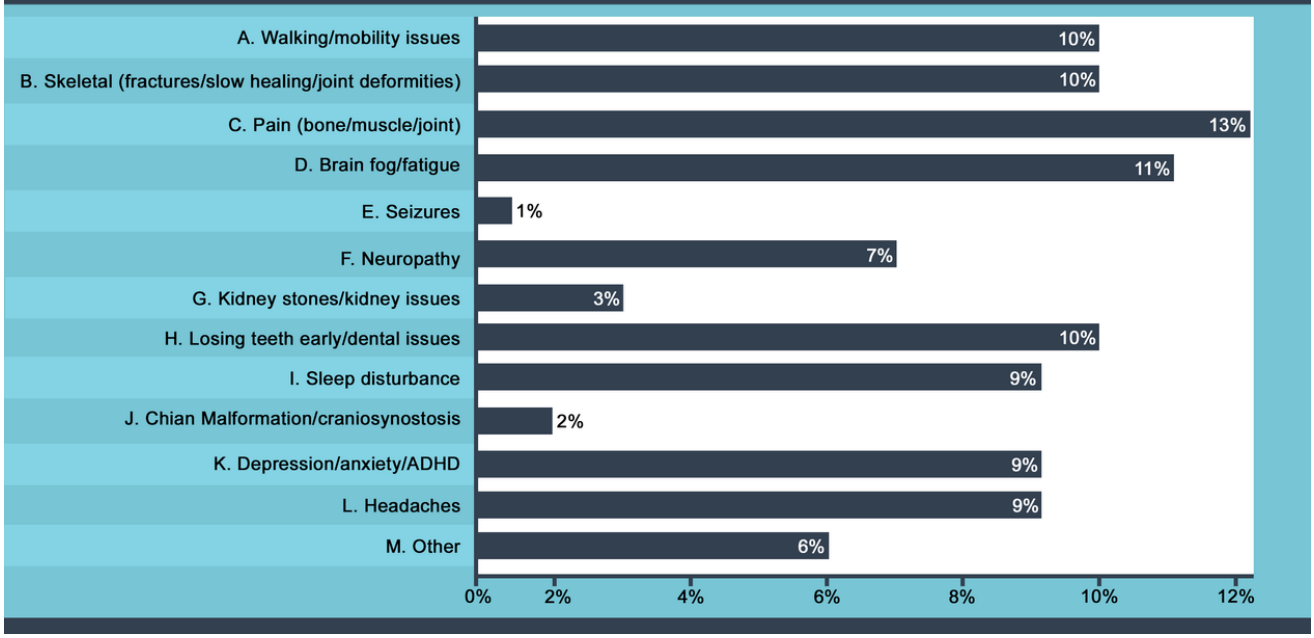
1. Which of the following hypophosphatasia-related health concerns have you or a loved one ever had? Select ALL that apply



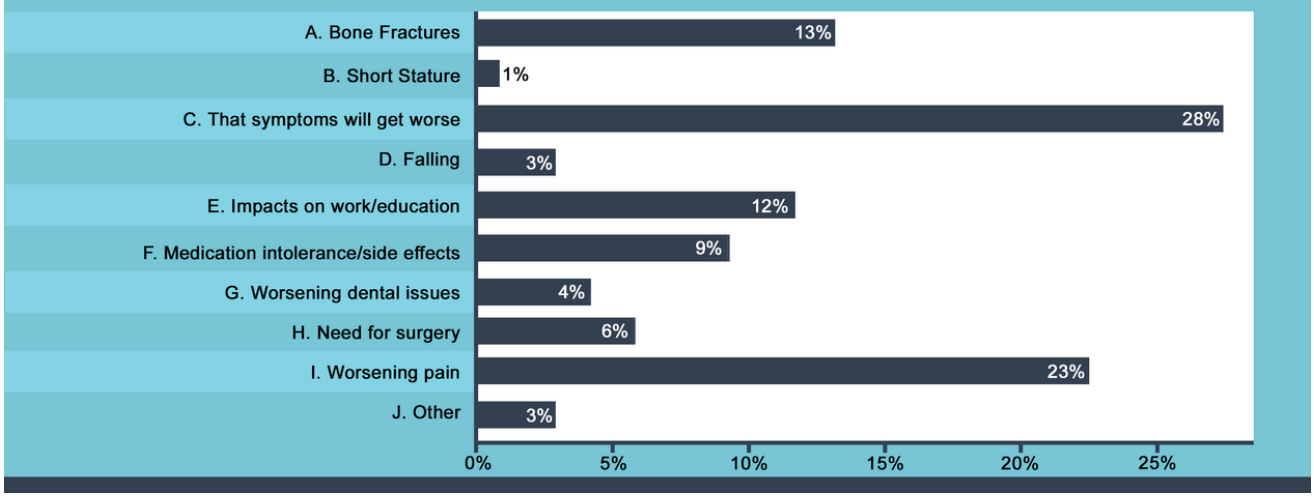
2. Select the most troublesome hypophosphatasia-related health concerns that you or a loved one have ever had (select top 3)



3. What specific activities of daily life are important to you, that you or a loved one that you/they are NOT able to do or struggle with due to hypophosphatasia? Select TOP 3

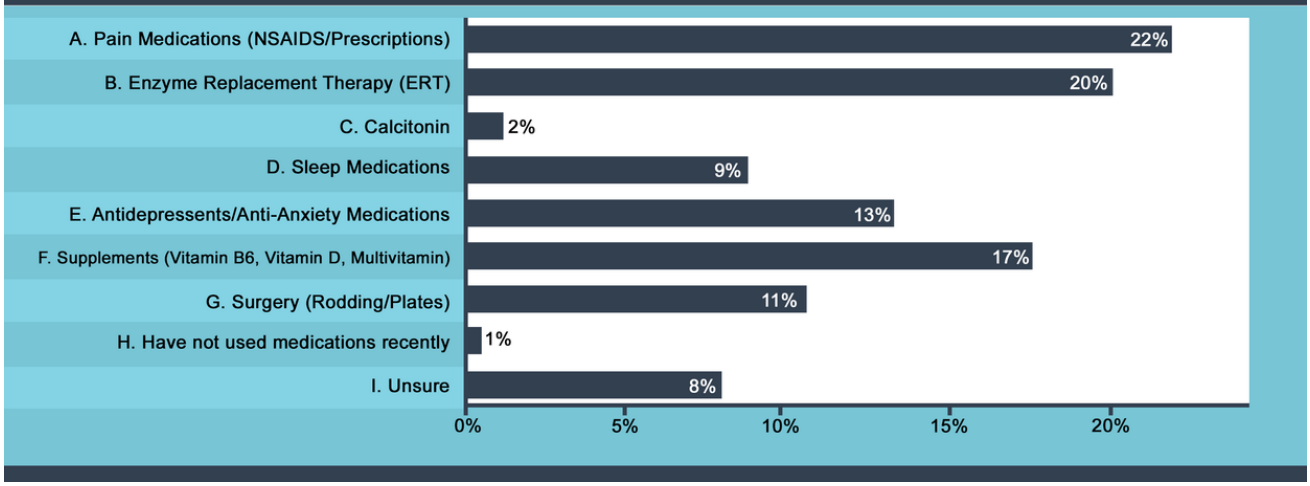


4. What worries you the most about you or your loved one's condition in the future? (select top 3)

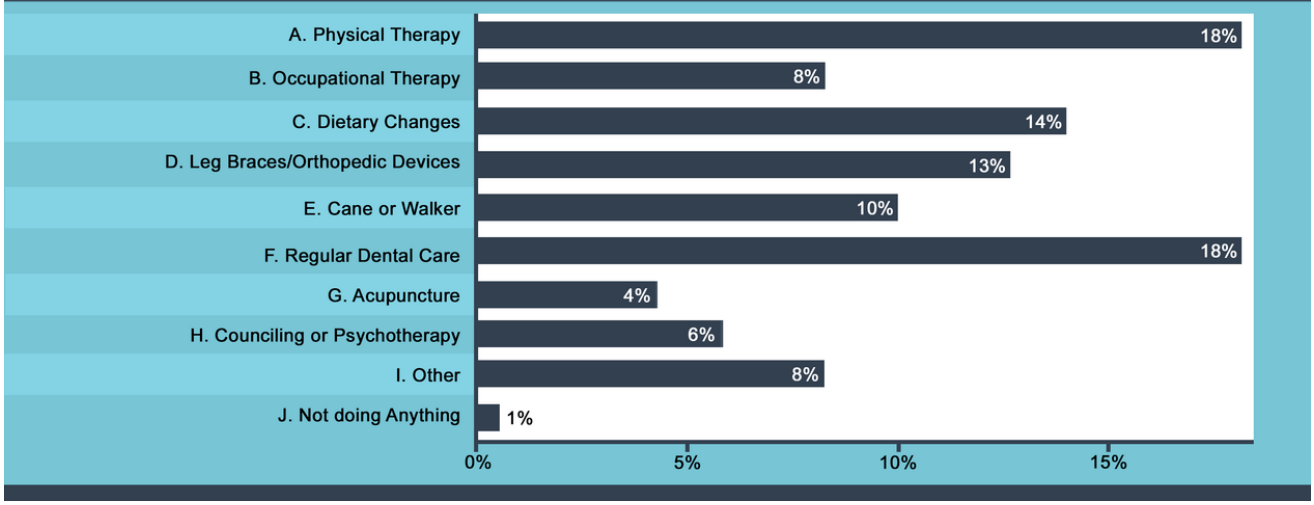


Topic 2 Polling Results

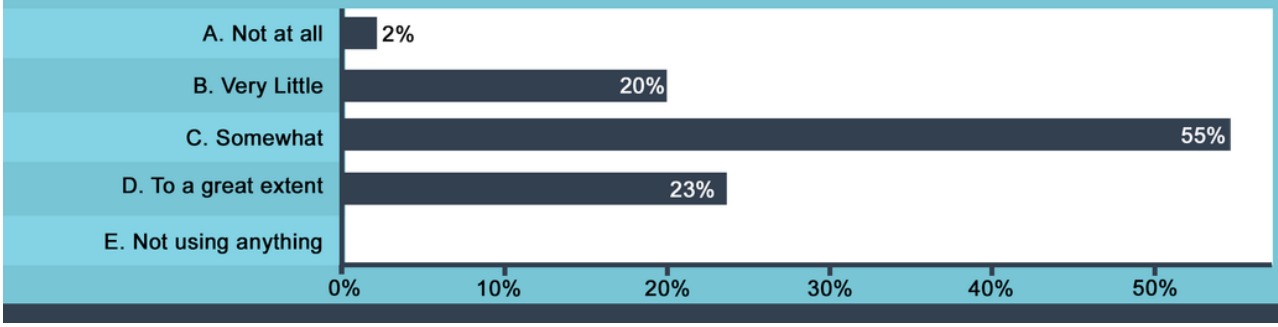
1. What medications or medical treatments have you or your loved one used (currently or previously) to treat symptoms associated with hypophosphatasia? Select ALL that apply



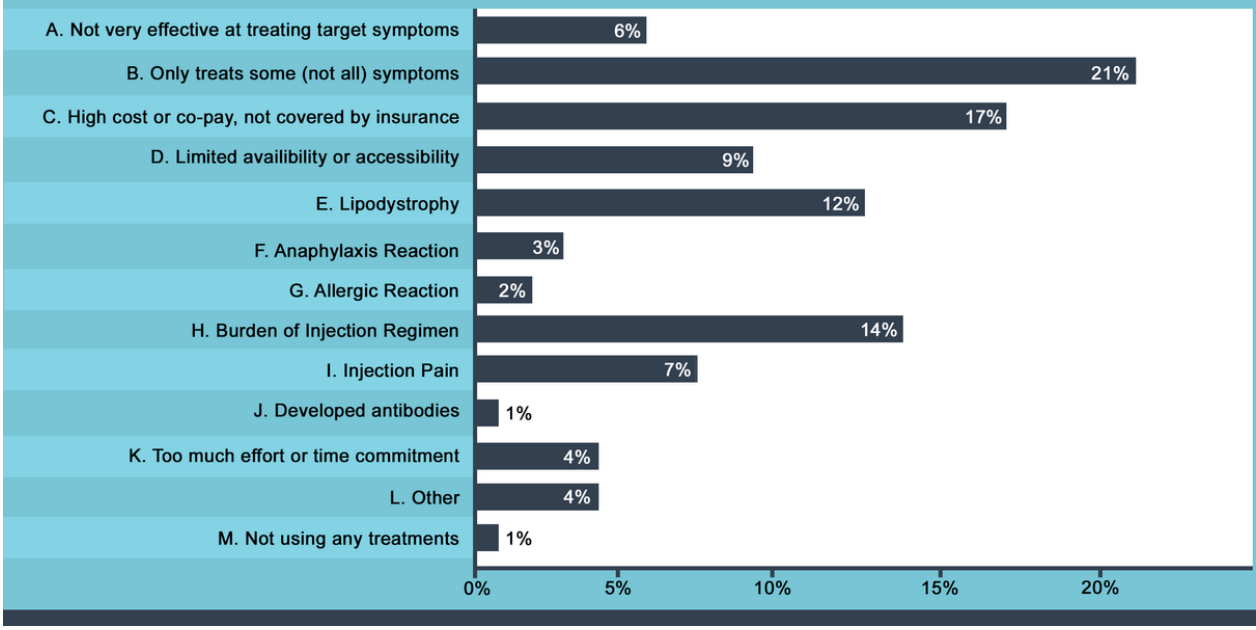
2. Besides Medications and Treatments, what have you or a loved one used to help manage the symptoms of Hypophosphatasia? Select ALL that apply



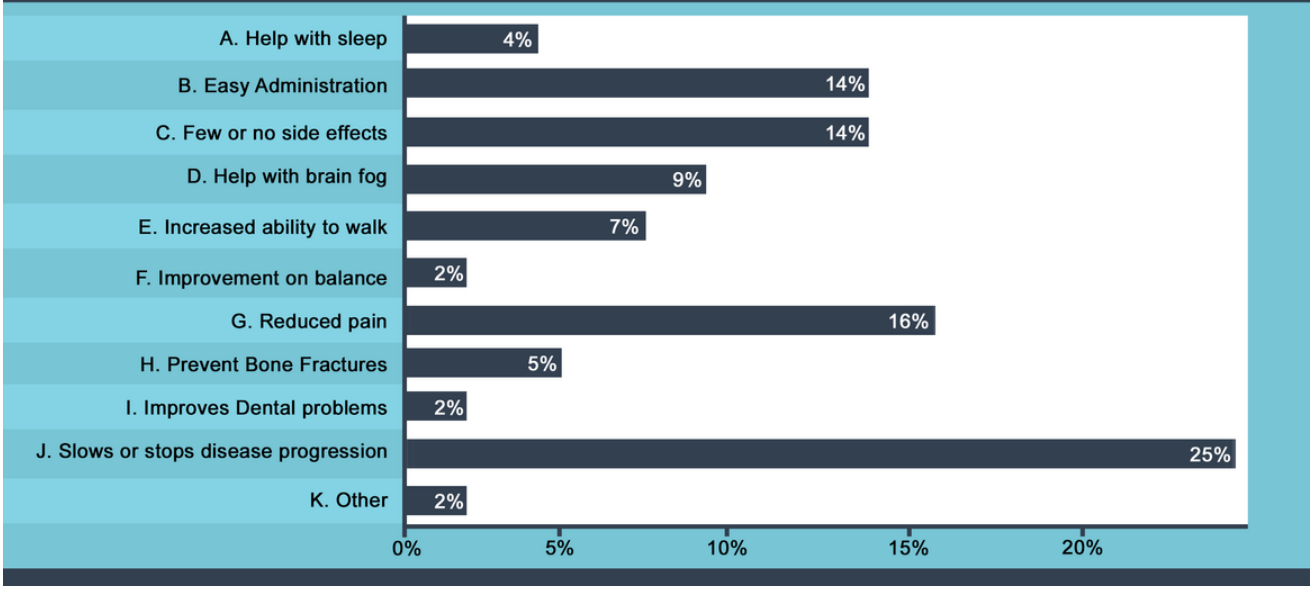
3. How well does your or your loved one's current treatment regimen treat the most signifigant symptoms of hypophosphatasia?



4. What are the biggest drawbacks of your or your loved one's current approaches? Select TOP 3



5. Short of a complete cure, what specific things would you look for in an ideal treatment for hypophosphatasia? Select TOP 3



Kyle

Significant symptoms: 1.Constant Fatigue/tiredness. 2.Muscle pain. 3.joint pain or muscle weakness.

Best day: I take a walk outdoors, run an errand, and help watch my 2 nephews/1 niece for a couple hours.

Average: I wake up as tired as when I went to sleep. Drink a cup of coffee, sometimes fall asleep on the couch for a couple more hours.I spend a LOT of time reading through medical papers/ studies on biochemistry. Also online class for my coding boot camp.

Worst day:[[before I was fired. Work refused to make any kind of ADA accommodation. Ignored all medical documentation. They assumed It was all lies and I wanted to party on weekends]] for two years, mandatory over time was BRUTAL. every 1 or 1.5 months, I worked two weeks of 7x12hr shifts in a row really broke me. My leg muscles would be so painful at night I would only get 2-4hrs of sleep.Muscle weakness worsened with too much activity/very poor diet. Had to take breaks after half a flight of stairs. Some weakness in my arms.

Loved ones are not very sympathetic to the fatigue/tiredness.

Symptoms have slowly gotten worse since ~20yo. I've been on ERT for a couple months and it hasn't helped much, yet. Moderating amounts of activity, Excedrine, and 5-HTP dietary supplement seem like they help some.

I suspect some kind of dysregulation in Adenosine /cAMP possibly reduce response from dopamine 1 receptors plays a roll in some forms.

Before I knew about HPP, my rheumatologist had me try RA doses of methotrexate. Very tired the first couple weeks, then ~1.5 weeks of feeling great. Waking up refreshed and not having to always try to stay engaged thought the day was wonderful. Then it started making me break out in haves all over and I eventually stopped taking it. (I've had delayed pressure urticaria and urticaria since child hood. Peaked ~18yo)

FDA people, know any groups that can help me start an observational study on HPP patients and the SNPs? It would be a gold mine for understanding wide spread aspects of biochemistry. Point out areas to treat common "inflammatory" disease.

Also develop a better ALP blood test. Scientifically, it's only valid for people with no mutations in TNAP. Treating it as the most significant and accurate measurement is bad science.

Wendy

How has your loved one's ability to cope with the symptoms changed over time?
I am no longer able to do what I want or when I want; but I am getting better at doing whatever I can when I can.

I have pain, it can be significant; but pain is not my problem. The majority of my pain directly correlates with my muscle function; followed by headaches, systemic inflammation; and nervous system. I will not take opioids, I am allergic to most steroids, and concerned about stressing my kidney or liver with non-essential medication.

I have benefited from the following modalities:
Compression garments help with pain, proprioception, vascular/circulation, muscles, joints, tendons, and dysautonomia symptoms particularly low blood pressure and heart rate dysregulation. It is important to find the right level of compression. The brain receives the sensation of compression faster than it receives the pain signal. Quality compression garments are expensive and finding the right type requires trial and error. I am partial to Intelliskin shirts and CW-X banded compression tights. I use different compression levels depending on what activities I will be doing and which symptoms are being managed.

Oxygen Therapy: 2-5L for 30 minutes 3x/day. Started in July 2022 via an Oxygen concentrator at home. Used for muscle fatigue, muscle function, muscle recovery, and potential to alleviate headaches. My Immunologist (specialist in Ehlers Danlos, Mast Cell, and Dysautonomia) provided the Rx and I purchased the oxygen concentrator out of pocket. I highly recommend Oxygen Therapy to anyone with muscle disorders, fatigue, pain, and systemic inflammation. Although Oxygen Therapy has not help with my headaches, it has been remarkably beneficial to me and many of my symptoms.

Hypermobile joints: custom bi-lateral knee braces, SI joint belt (pelvis), finger ring splints, Ottobock Omo Neurexa bi-lateral Orthosis, Ossur Unloader Hip Brace, along with various other hand, ankle, wrist, elbow soft support. Other stabilizing orthotics as needed for joint recover post injury or subluxation.

Body Braid, Arm Braid: https://bodybraid.com/ A brilliant body support system. Might not work for everyone, but worth trying to find out. This is an elastic, full body, dynamic support system that aids with proprioception, joints stability, and tendon support, muscle recovery, posture alignment and strengthening. It needs to be introduced gradually and will help your body regain posture, strength, stability. I have been able to regain some core stability with the Body Braid, which is an area that suddenly lost strength and has been incredibly difficult to regain. I am also able to use the Body Braid during aquatic therapy which is not possible with most joint braces. The Arm Braid enables me to use my cane, arm crutches, Nordic poles, and rolling walker longer. It also allows me to drive short distances, open doors, fold clothes, and do range of motion exercises occasionally.

Mobility aides: Smart Crutches (adjustable forearm crutches); cane with stability foot, rolling walker with seat, and Nordic walking poles. Pillows to support joints when in bed. Power lift recliner with infinite positions has been life changing. Perch sitting (look it up) has been beneficial to me; it has helped strengthen my core and helps my posture. It also required a very gradual introduction. Sit/Stand desk, although my vision and cognitive prevent me from doing much on the computer. Reacher/grabbers for the million things I drop and can't pick up. Shower chair. Several kitchen aides: ergonomic knives, different gadgets to open jars, twist to open, or pull tops, racks to hold pans individually and upright, pull out shelves, and ADA appliances. My car has smart cruise control and other aids that allow me to drive short distances on the few days I am functional. I might benefit from a motorized chair when/if I am able to leave the house more, but I am not currently able to sit very long.

Meditation and Breathwork: while these will not fully resolve or prevent pain, brain fog, or dysautonomia symptoms they do help significantly.

TENS unit, heat, cold packs, massagers, massage, acupressure, various gadgets to relieve tight muscles, knots, and trigger points. Any ADA, Ergonomic, Arthritis, similar aides and accommodations: easy open Rx lids, pens/pencils, utensils, pump tops on soaps, shampoos, lotion and large flip tops on toothpaste.

Physical Therapy has been one of the more challenging aspects of my HPP life. Most Physical Therapists are programed for acute injury or post surgery recovery. The physical set backs and mental torture I have subjected myself to at the hands of countless Physical Therapist is staggering and shameful. Doctors don't believe you want to get better when not actively attending Physical Therapy. Too many Physical Therapists do not understand the nuances of chronic conditions and muscle disorders. Deconditioning is not variable, but my muscle function is highly variable. Fortunately, I have been physically active most of my life and with the guidance of one exceptional Physical Therapist have been able to start and maintain a Home Exercise Program https://www.hep2go.com/ particularly with aquatic therapy.

Aquatic Therapy: I am able to stretch, exercise, and relax during aquatic therapy. Since being on Strensiq I am able to do much more strengthening in the pool and have recently started simple supine ROM exercises on land. When I unintentionally do too much I am able to speed up recovery with aquatic therapy.

Nordic Pole Walking: It took me over a year to be able to coordinate my steps with my arm movement and I was only able to work at it for a few minutes at the beginning. It has been extremely beneficial in improving my posture, gait, stability, and stamina. My current goal is to go outside every day to Nordic pole walk.

Psychologist and support groups: HPP life ain't easy. Take care of your mental health, no one else can do that for you. Do not burn out yourself, friends, family, and care team. Managing an unpredictable chronic illness requires constant effort both physically and mentally. We cannot always be our best self when our body and mind fail us. It is worth the time and money to keep a healthy approach, work through the trauma, process the grief, and let go of whatever is not helpful.

In order to be functional for doctor appointments I have to limit my physical activity and mental demands for several days prior to the appointment. Unfortunately, when doctors only see you at your best, they cannot understand just how debilitating the condition is on regular days. If I don't rest up prior to the doctor's appointment, I am unable to effectively communicate and fail to optimize my very limited time in front the doctor. This is frustrating for me and must be difficult for the doctors as well. In between appointments, I also keep a running list for each doctor and add questions/issues to the list so I am prepared for the next appointment.

Challenge: Building the Care team of doctors and medical professionals. Finding the right doctor that is knowledgeable and accessible is not always in-network. Some of my best doctors are not Specialist in my conditions, they are just excellent doctors who listen, care, and have become integral to my success. I have encountered Specialist who are unwilling to diagnose, acknowledge, or treat symptoms.

Heath Insurance – I have coverage under my husband's employer. So far they have approved and covered Strensiq, IVIg, Dupixent, my in-network doctors, and most of my covered Rx medications. I have to pay out of pocket for all out-of-network doctors, many of my medications, supplements, compression garment, oxygen concentrator, aquatic therapy, all of my mobility aids, and so many other aspects of my care. This year I have to appeal denied claims for routine blood labs, my in-network Psychologist, and covered Rx medications. This terrifies me because I cannot afford to pay for Strensiq or even IVIg; these are my main treatments and without them my body does not function.

The paradigms that make all this so difficult to understand, manage, and treat:

What is causation? What is correlation? What are Symptoms? What are Reactions? Where do you start? Who can help? What is covered by Insurance? What can I afford? Can I get the correct diagnosis to be eligible for the right clinical trials? If I participate in one clinical trial will I be disqualified from other clinical trials?

Metabolic, Autoimmune, Hydrocephalous, Connective Tissue, Dysautonomia, Mast Cell, Joint formation, Hypermobility, Vascular...

Thank you to everyone involved in making this EL-PFDD possible. I feel like the luckiest cursed girl.

Benefits and challenges of current treatments?
I had sudden symptom onset in early 2017 which rapidly became debilitating by the end of 2017. My first symptoms were gastro, muscle disorder, muscle fatigue, muscle cramps spasms, along with a wide array of autoimmune issues impacting central nervous system, including vascular, skin, cognitive, and dysautonomia. The muscle dysfunction rapidly lead to joint instability due to hypermobility. I had muscle, tendon, joint, bone, skin pain along with migraines, vision disturbances, gastro distress, and cognitive decline.

Rx, medications, and supplements:
Acetazolamide: 125mg 3x/day for muscle function. Taken from May 2018 to May 2022. Prior to Acetazolamide my muscles and tendons were extremely tight all the time; my muscles would constantly cramp and spasm. I was not able to do anything during aquatic therapy without going into severe muscle spasms. After 3 months on
Acetazolamide I was able to do light stretching in the pool. My muscle tightness, cramps, and spasms eased a little. While symptoms were still severe and debilitating the slight improvement and ability to get temporary relief in the pool was valuable. I wonder if Acetazolamide might have helped hydrocephalus and will discuss with my medical care team.

Cyclobenzaprine: 10-20mg /day at bedtime since July 2017. This has been the most consistent help for my muscle disorder. I am not able to take it during the day, but it effectively relaxes and resets my muscles every night.

IVIg: since January 2019 for Autoimmune symptoms. I have been on high dose IVIg,140mg every 3 weeks. The infusions are for 3 full days at home. While the IVIg infusions trigger my mast cell reactions it has resolved some of my autoimmune symptoms and continues to manage and improve others. My muscles are less tight and do not cramp as easily. The mast cell reactions are harsh and numerous. I have only begun to mitigate them in the last year and half.

Dupixent: since August 2022, 1 subcutaneous shot every 2 weeks. Replaced Xolair which was started in July 2021 prior to starting Strensiq in November 2021. Dupixent is far more effective for me than Xolair. Both Dupixent and Xolair trigger my mast cell reactions, but also help manage these reactions. For example, I have not had blistering rashes on the palms of my hands since I started Dupixent; and my scalp gets warm but I no longer need to apply Pimecrolimus cream and use ice caps everyday. Xolair is a pre-filled syringe, I had two incidents with dull needles which left me too stressed to self-administer with pre-filled syringes. When I changed to Dupixent the Rx started with pre-filled pens, similar to an Epi-pen, think large spring loaded – very painful. The first Dupixent dose went into my thigh muscle and took over a month for the knot to dissipate. The pre-filled pens are harsh, painful, and there is no way to control how deep the medication is injected. Thankfully, I was able to switch to pre-filled syringes for Dupixent and my husband is able to administer this medication.

Strensiq: since November 2019, 3 subcutaneous shots per week. The shots trigger my mast cell reactions and I also have delayed injection site reactions. The first week on Strensiq it was immediately easier to move and my daily step count increased. After 6 months on Strensiq my vitamin B6 levels were normal. My muscles still fatigue and dysfunction; but recover much faster. I have to juggle the timing of IVIg, Dupixent, Strensiq, and Covid Vx boosters because they all trigger my mast cell reactions. If I go more than 4 days between Strensiq doses my muscles rapidly begin to tighten up, cramp, fatigue, and dysfunction. Because I have delayed injection site reactions to Strensiq, I use a medical grade skin marker to indicate injection sites and avoid over lapping sites. I also use the micro-needles which work very well for me and my husband is able to administer Strensiq in my arms and buttocks. My injection site rotation can be complicated by general inflammation in my thighs from autoimmune symptoms and also accounting for Dupixent injection sites. So far we manage.

Tacrolimus Ointment or Pimecrolimus Cream are very effective for my injection site reactions from Strensiq. My injections site reactions are delayed, within a week or two the site will become red, firm, and painful. These reactions can last up to 2 months and are worse when my mast cell reactions are triggered.

Voltaren (diclofenac) gel was mildly helpful, but Tacrolimus or Pimecrolimus are much more effective for me.

Low Dose Naltraxone (LDN): 4.5mg /day since January 2021. Provides significantly improved sleep quantity and quality. Originally started LDN trial to see if it would help with Autoimmune symptoms or provide pain relief. While it did not make any noticeable impact to autoimmune or pain, I continue taking it for far reaching quality of life benefits of improved sleep quality.

Aspirin LD trail: After discontinuing Acetazolamide, it was recommended I do a trial of Low Dose Aspirin for joint swelling, systemic inflammation, and as a mast cell stabilizer. While Aspirin was highly effective in easing joint bone pain and systemic inflammation; unfortunately, it resulted in bleeding gums and caused existing petechia to be much worse. It has been recommended, and I will next do a trial with Willow Bark instead of Aspirin.

Mast cell reactions and Metabolic function are so individualized in both triggers and mitigants. I continue to work with Immunologist, Allergist, Hematologist, Dermatologist, Rheumatologist, Neurologist, Internal Medicine, and Nutritionist to best manage my reactions. In addition to pre-dosing with a variety of anti-histamines, mast cell blocker and inhibitors; I also need to take several daily. I have modified my diet and have to monitor my kidney and liver to ensure I am not over taxing my system with medications. Everything is trial and error. We do our best to make only one change at a time so we can determine what is helping and what might be causing problems. Everything is a constant effort to balance benefits over risks.

Metabolic function: I think it is critically important to find a health care provider that understands the need of monitoring vitamin, nutrient, hormone, and blood levels. When my symptoms started in 2017 my vitamin D level was undetectable, my ALK was very low, and my CPK was elevated. My Vitamin B6 level was not checked until 2021 and it was very high. I have since found out my B12, Riboflavin, Magnesium, and other levels are too low.
Since being on Strensiq my B6 levels are normal, this aspect alone needs more focus. Strensiq is not only for brittle bones, it is also fixing the metabolic dysfunction. I have every reason to believe I will continue to regain physical and mental function.

Struggles include the need for specific diagnosis of various co-morbidities. Without diagnoses, we will not qualify for some clinical trials and/or get appropriate care and treatments.

Need Specialist that are in-network or have the ability to get gap exceptions for sub-Specialists.

More support to families to get tested and educated. I feel like I failed to properly explain HPP to my brothers. One brother seems to be symptomatic. My other brother and his sons also declined free genetic testing. That was a lot of pressure on me to be the spokesperson and explain the significance to my family at the same time I was newly diagnosed and doing all I could to navigate my daily life.

My Mom did agree to genetic testing and is finally diagnosed with HPP; she lives in a rural area and her ability to see specialists and get appropriate health care are big concerns.

Are there specific activities that are important that you or your loved one cannot do at all or as fully as you would like because of Hypophosphatasia?
The symptoms are so vast, unpredictable, and far reaching.

Acute symptom onset in 2017, at the age of 45, I rapidly went from a highly active person who enjoyed hiking, kayaking, cross-country skiing, pilates, major home improvement projects, landscaping, making firewood, framing artwork, various craft projects, able to use power tools, various hobbies, and dancing. I really miss dancing; and sex. Driving a manual shift vehicle and road trips to visit my family who live all across the country. I worked 18+ years in finance, was active in forming/leading a public speaking club, and volunteered in animal rescue. I was the person who would take the stairs instead of using elevators.

In early 2017 my symptoms started with muscle fatigue and cramps, followed by a wide variety of autoimmune symptoms, severe joint instability, significant dysautonomia symptoms, vision disturbances, central nervous system dysfunction, vascular issues, mast cell disorder, insomnia, gastro issues, constant headaches, severe pain (muscle, tendon, bone, joint, and skin) and cognitive decline.

By the end of 2017 I had to leave my career, move into my guest bedroom because I could no longer manage stairs. I require pillows to support my joints when laying in bed to prevent subluxations. I was not longer able to sit in a regular chair, stand or walk unsupported, bend over, lean forward, or change positions in bed without severe muscle cramps and spasms. I could not walk on uneven terrain, walk against a gentle wind, or a make it up the slightest incline. I can fatigue getting dressed and have to take breaks. My hands would collapse when I tried to plug or unplug an electric cord. My fingers would bend backwards trying to open a zip top bag. I could no longer use a broom without full body cramps and severe tendon pain. I could not use a hair dryer. My hands will stop working and fling or drop what I am holding. Neuropathy in my hands and feet presents as numbness and tingling which also impacts my mobility, stability, and dexterity. Occasionally I have sudden sharp stabbing nerve pain which can occur anywhere in my body, at any time. I am no longer able to drive myself to most medical appointments; which means my husband must take time off from work. Even for tele-video appointments, my husband needs to attend in case my cognitive function fails me. At times I am not able to turn my head; other times my muscles or joints lock up. Temperature dysregulation, rashes, visions disturbances, muscle dysfunction, joint instability, blood pressure, heart rate, vision, respiratory changes, gastro symptoms, systemic inflammation, etc.

My HPP symptoms are predominately metabolic; I do not have brittle bones or bone density issues; but I do have joint issues. I have bi-lateral hip dysplasia, Osgood-Schlatter lumps on both knees and similar on elbows and TMJ that has caused my jaw to lock-up. When I was diagnosed with HPP, I was also confirmed to have hypermobile EDS. Most of my joints are hypermobile which I have managed throughout my life by strength training to provide stability, posture, and function. When my muscles dysfunction started in 2017 I was no longer able to maintain joint stability and I was prone to constant tendonitis and subluxations. I now have to use braces and various joint support for my hips, pelvis, knees, ankles, fingers, elbows, shoulders, wrists, and back.

Since symptom onset in 2017, I have been diagnosed with Hydrocephalus, Mast Cell disorder, Dysautonomia including autoimmune Small Fiber Neuropathy, Autoimmune Channelopathy and UCTD, Alopecia, in addition to hEDS, and HPP. It is not clear what are symptoms and what are reactions to my treatments.

As a child I had significant “growing pains”, migraines, insomnia, early tooth loss, excessive cavities, TMJ problems, hyper-sensitive teeth, under-developed permanent teeth, delayed reading and writing, below average physical ability/strength in elementary grades, weak upper body all my life, sweating disorder, frequent bronchitis, periodic times of being unwell and prone to GI distress. There are other childhood symptoms that I do not recall at the moment; but I was a highly functional human until symptom onset in 2017.

Strensiq is restoring my muscle function and IVIg is helping my Autoimmune symptoms. While I am still extremely limited, I am making real and measurable progress since starting Strensiq. My teeth are less sensitive for the first time in my life.

It is all the little big things that matter now.

How does Hypophosphatasia affect you or your loved one on best and on worst days? Describe your best days and your worst days.

HPP impacts every aspect of my day and has completely changed my life.

Best days include some, but never all of the following: taking shower, being able to walk around my house all day, navigate stairs, Nordic pole walking outside, aquatic physical therapy, able to cook meals to put in the freezer, read print or work on computer/tablet, pay attention to audio content, drive short distance to local doctor appointments or go to drive thru pharmacy, connect with family and friends, spend time with my husband, work on medical care management, figure out ways to do more things.

Worst days include the following: debilitating headaches, light and sound sensitivity, dysautonomia symptoms (so many) that keep me in bed or in the recliner, not able to communication. Not able to see well enough to do meaningful tasks or leisure activities. Rapid and sudden muscle fatigue or muscle dysfunction, joint instability. Muscle, tendon, bone, joint, skin pain. Nausea or gastro distress. Not able to start or finish tasks; either medical care management or personal needs. Not enough function to complete necessary tasks and never having enough function for the fun stuff. The absolute worst is the physical/mental setbacks after choosing to do one task over others and then not being able to do anything at all until symptoms ease. Also devastating is meeting the wrong doctor: all the prep of gathering medical records, creating a concise history, husband taking time off work, the physical struggle/challenges of getting to the doctor's office, and then that moment it becomes clear this doctor is not going to help

Of all the symptoms of Hypophosphatasia, which 1-3 symptoms have the most significant impact on you or your loved one's life?

1) Physical limitations, loss in muscle function, and rapid muscle fatigue impacts every aspect of my life. I have made modification in how I do almost all daily tasks, require braces or joint support on the majority of my body, need a variety of mobility aides, and am not currently able to do most ot the activities I enjoyed doing most of my life. Humans identify themselves by the activities they do. I lost all those activities and continue to discover who I am now.

2) Cognitive changes. It's more than brain fog. Many of my symptoms are a result of central nervous system involvement. This is so far reaching and it is not clear what is autoimmune, CNS, dysautonomia, pain, vision, vascular, or some combination. At times I am not able to comprehend, form thoughts, make decisions, tolerate certain sounds or tones, convey my thoughts.

3) Loss of independence due to the variability of symptoms and function. I never know when or how long I will be functional. This makes it impossible to have a schedule, daily routine, or make plans. Not knowing what my body or brain will allow me to do at any given time.

My symptoms came on suddenly in 2017 and ended not only my career but prevented me from doing all the activities I enjoyed and took all aspects of my life that defined my personality. I was told all my symptoms would resolve after my Vitamin D levels became normal. That was not the reality. I am now on permanent Disability, which I am tremendously grateful for; but I would rather be an independent and functional member of society.

Jennifer

We adopted our son from China when he was 2 1/2 years old, and he has struggled with gait issues and teeth loss since then, and he is now 9 years old. He was diagnosed with HPP when he was 3 years old. We went to see Dr. Whyte and his team at Shriner's Hospital in St. Louis from 2016-2020, these visits were typically every other year, until the funding ran out and they closed the clinic. Our son struggles with walking, and anything more than than makes him out of breath and exhausted. He went to a new doctor in Dec 2021, and his bone density levels were found to be significantly worsening, and he was prescribed Strensiq.

He started in November 2022, and we are just beginning this journey. 2x days injections are incredibly hard for our warrior Zeke. He screams and does not want to have them. We know he needs them, and so we compassionately encourage him through these injections. We would absolutely love a different option for a route of medication--anything other than injections. We are hopeful that Zeke will begin to feel the benefits of the therapy in the next couple of months, as this will help him stay brave and courageous.

Thank you for all you do!

Sharon

1. For Hypophosphatasia pain, fatigue and mobility issues impact my loved on the most.

2. Worst day curled up in bed sleeping for most of the 24 hours in the day or for days. Pain fatigue sleeping more due to these things. Less activities and work, family time, social time,travel that he would love to do. Pacing himself for the week versus the day. Using mobility devices such as cane, Walker, wheelchair, electric wheelchair depending on the day.

3. * Yes
 * It impacts everything (can't work because of many fractures in a short period of time and no treatment at the time. I was in my forties. It was shocking)
 * unable to work, less family,friends and social time. An unending pain
 * Best day able to get up, move around,see family friends, get out of the house, closer to a normal life but even on my best day I don't do everything I want to do. I probably do about 40% of what I would like to do.

How has your loved one's ability to cope with the symptoms changed over time?
It is difficult the longer it goes on. It's a lot of stress. Before Strensiq you weren't hardly coping. Strensiq provided a way to do things and cope better with life again. It helps to do more cope more and enjoy family more. If I would have had this drug years ago I would probably still be working but I am thankful for now. Before Strensiq I was like Rip van winkle or a bear hibernating for winter. The storms or cold weather make it worse and rest and heat do seem to help. but some days I would sleep most of the day. This cuts back on activity and getting out of the house and enjoying life due to pain and fatigue. Once you spend your energy it may be gone for several days so I plan activities not just for day but in looking at the whole week.

Janet

I just got diagnosed at nearly 65 and told Im not eligible for treatment due to age and risk. I was diagnosed and treated with the absolute wrong medication for years. Is more being done to provide treatment for those if us older folks especially the side issues that come with HPP.

Holly

Pay attention to the Driscoll girls. They know that even with pain, life needs to go on. All “ rare” diseases need to be addressed.

Autumn

I'm a caregiver to a two year old girl with HPP. One of the hardest symptoms of HPP was the craniosynostosis that developed and the surgery that was needed because of it. It has created long-term anxiety for my daughter at the doctor's which makes it difficult to take her to appointments.

My daughter is unable to keep up with kids her age. She is smaller and tires more easily than those in her age group. Watching her disappointment of not being able to participate in some activities with other children can be heartbreaking.

Due to Strensiq, my daughter's HPP has drastically improved, however, I hope for the day of a better solution. She gets anxious with every injection and she gets bad site reactions.

Carol

I was diagnosed with HPP when I was 67. I couldn’t believe that all of these years of chronic pain and surgeries finally had a name.
I lost teeth at age 11 due to gum infection that almost killed me. I didn’t have enamel on my teeth, therefore my teeth didn’t have a seal on them to prevent infections. I end up with a partial at age 11. It was horrible. I have TMJ so bad because all of the partials.

I was in and out of the hospital as a child. I had unexplainable urinary problems and still do.
My journey was a rough one and was considered a hypochondriac by many. It was so hurtful because I suffered so.
I had six shoulder surgeries with the last one a total replacement. My joint had worn down in four sides creating a diamond shaped ball joint. My shoulder would pop out and it was so painful. I end up with a knee replacement and meniscus tears in both knees. The brain fog was bad some days and I didn’t understand it. I could go on and on but the fact is, this is a horrible disease which creates so many problems, especially pain all of the time and worse at bed time. This disease needs to be more recognized and helped. Thank you for you time.

Sandy

1. Pain all over, IBS, not sleeping good.

2. On best days your able to do things but at slow pace. Worst days, don't have the strength or energy to get up and move.

3. Going camping, setting up and breaking down camp.

William

1) aside from the obvious fractures and arthritis that comes with HPP, I feel like sleep becomes extremely inefficient and you get all the symptoms of sleep deprivation like fatigue, anxiety, and trouble thinking. This is arguably worse than the fractures and arthritis.

Tracey

Have severe pain.
Weakness in the muscles.
Feel so exhausted all the time.
Very emotional and depressed.
Can't read due to eyes blurring.
Can't concentrate.
Hands are swollen,weak and painful. Drop items all the time. Terrible burns.
Feet are in agony and swollen,can't wear shoes.
Have to use crutches and a wheelchair.
Feel like I am really unwell.
Kidney and gallbladder problems.
Headaches.
Heart palpitations and chest pains.

Matt

Hello again, My daughter and I were recently diagnosed and still learning. From what we have heard previously, as well as in this forum, it seems like almost any malady anyone with HPP is suffering is being attributed to HPP.Is it really possible that HPP alone causes all these problems? And if it is, then why does Strensiq not solve them all? Tks.....

Ann

HPP has impacted me since birth. I wish it was easier to get approved for treatment with Strensiq. I appreciate the help it gives me with my bones but would appreciate increased mobility and increased energy and abilities and less pain. I am doing so much better with the treatment, but I worry every year that I won't get approved for treatment for the next year or will lose the assistance I get with copays as it would not be possible to continue. I wish I didn't have to take 6 shots a week.

Tarin

Injection sites are not great. A pill would be much better or reduced injections.
Being short stature has more difficulties. Headaches are debilitating and the fatigue.
Great session today from both of you and all the participants.
Thank you

Lara

One of the treatments for hormone issues is tiny, slow-release pellets that can be injected underneath the skin of the hip....I think once every six months or so. Could ALP be administered that way?!

Kristina

We have chosen to stop treatment with Strensiq for our child due to the stress of injections and side effects. I would love to see a less invasive treatment option.

Alison

Similar to the panelists, for treatment, would love to have the following:

- less frequent injections (I do 2 injections 3x per week). If could do 1x per month or 1x per quarter would be great.
- easier administration
- temperature control

I dislike doing the injections so much that I'm exploring the gene therapy clinical trials.
Thank you!

Lara

I'm concerned that it doesn't seem like there has been very much research about the efficacy and safety of the standard dosage recommendation for Strensiq. My Mayo doctor is not certain that adults need the same dosage as infants whose bones are still developing. He, therefore, started me conservatively at one-third of the standard dosage. That was enough to resolve the issues I was having. I wish dosage would be further studied.

Stephen

I also wanted to comment on the dental side.Our kids were diagnosed by the Orthodontist as very young kids. Kudos to him for caring. We are mild impact HPP but even as mild finding a really engaged periodontist is a very important part of our care strategy.

Suzanne

I'd love to see a treatment option which does not require refrigeration. Having to keep our medicine at a consistent temperature is a constant worry. Traveling is stressful, or not possible.

Susan

Would love to see a new treatment that reduce the joint stiffness and tendons calcification from happening. So if I do fracture I can still be busy with my hands working and on crafting.

Matt

Hi, The potential use of Strensiq has been suggested by some doctors we have seen, but our understanding is that it is enormously expensive. How do most patients (who aren't very well-to-do) manage to obtain it at a reasonable cost?
Tks.

Alison

Hi - I wanted to provide some comments on treatment:

- I'm thin (100 lbs) and the injections are very painful for me. Rotating injection sites but still painful and skin is tender/sore post injection for up to 2 weeks after.
- I get a lot of knots under skin post injection. I've been using Arnaca creme to help.

Like another caller, I have been having more heart problems - having heart arrythmias since being on Strensiq.

My biggest concerns with Strensiq is a) affordability/cost over time as I'm self-employed and worry about being able to afford it long term b) how it is affecting other organs c) the high ALP now in blood and how that might affect liver and other organs, etc.
Thank you!

Millie

I take the full adult dose of Strensiq, 3X per week. The Strensiq is thick to inject. My husband injects me, and it takes about 30 seconds to empty the syringe on each side. He cannot push the syringe against my skin, and holds the syringe steady before it feels like he is pushing too hard. How do parents inject their children quickly. That would hurt a lot!

Ed

I was on a one year trial 2015-2016. I was on crutches full time and near the end of the trial, I would sometimes wonder where I left one of my crutches as I was getting stronger. Then, the trial ended and the regression did not take long at all. I wish it was available in our country and I would encourage those who are afraid of starting stensiq treatment, don't hesitate. It could change your life before it's too late as it does not reverse all the previous dammage HPP has or will do.

Debby

Traveling with Strensiq is quite challenging because of its refrigeration requirements.

Marie

I am 71 years old and have experienced several bone fractures in ankle and spine. I am affected by mild to moderate pain in my lower back. I also have some balance issues. Meclizine helps.I was finally diagnosed with HPP 10 months ago (referred to endocrinologist) after decades of worsening bone density despite decades of on and off use of fosamax. Going back through my medical records, we found that my alkaline phosphatase has been somewhat low since the 1990s.
I am appreciative of receiving the correct diagnosis. I am injecting Tymlos daily. This will be for two years and then I will have another bone density scan.

Amy

The high cost is a continuous worry. It makes it hard to get prescribed. The insurance always may not cover it in the future. It is hard to get approved and I needed reapproval at 6 months. The insurance demands records that are unreasonable old or unreasonable proof of improvement in an unreasonably short time period. Doctors don't want to treat us because insurance companies are too demanding and take too much time to get these expensive medicines approved. It is an extremely stressful process.

Tracy

Develop an asfotase alpha patch (removable)

Jenifer

Strensiq does help, I am not sure I would be able to walk without it at this point, but for 2 of my kids and me, we are unable to take aspirin or NSAIDs because of a comorbid bleeding disorder. Pain therefore, is still an issue as well as other issues that are helped by Strensiq but not eliminated.

In the future, and as Sue and Canon mentioned, I hope that a different administration of the medicine will be developed in order to address the lypodystrophy. I also hope any doctor who chooses to go into orthopedics is required to know about this disorder so they are informed when they treat HPP patients.

Lastly, I hope someone figures out what the excess amount of ALPL causes that manifests in our bodies due to treating with Strensiq as such high numbers are concerning.

Laura

As someone who is allergic to NSAIDS along with many other medications that would keep my pain, muscular and anxiety at bay, I have very few options for drug treatment outside of Strensiq to help with my HPP. A month in with enzyme replacement therapy, I am hopeful.

Lara

I responded that Strensiq has helped me to a "great extent" because my brain fog, fatigue, peripheral neuropathy and bolts of nerve pain are much better.

Other things I do for treatment:
Exercise--prior to my diagnosis, I had stopped exercising because my joints were grinding so much (probably due to CPPD) that I thought exercise would make my joints worse. When I finally got to a rheumatologist, I learned that it was better to continue exercising despite the grinding. After starting Strensiq, my joints do not grind nearly as much.
--Dietary changes:
No dark colas because they're high in phosphorus
No fortified cereals because of vitamin B6
No more multivitamins because of vitamin B6
Try to eat low-sugar and anti-inflammatory foods and beverages
I opted to start Strensiq to relieve symptoms and in hopes of preventing decline. My grandmother had severe osteoporosis and horrible problems with her feet and teeth, all thought to be related rheumatoid arthritis, but my genetic tests indicate that she probably actually had HPP.
Although I'm very grateful to be on Strensiq, it's far from a great solution. I have the same problems everyone else has mentioned: painful, burning injections; huge sore, hot, red injection locations for the first four months; increasingly leather-like skin that is hard to inject, and lipodystropy with purple lumps. It is also very difficult to travel with Strensiq, and we travel a lot for our livelihood.

Mel

I said somewhat because Strensiq has helped significantly with the long bone pain and severe fatigue but it hasn't been able to fix my degenerative tendons which have developed over the last 63 years.So I am still severely limited with my mobility. I have only been on Strensiq for 3 years though. I feel that Strensiq has stopped the disease in its tracks - prior to the medication I visited 50 specialists over 7 years since diagnosis and had 4 surgeries. Since being on strensiq I have only had monitoring visits to my specialist.Have reduced my medication for mental health, am no longer on opioids and haven't visited my GP once for the condition! I also ride a recumbent trike in order to try and retain my strength and function - its not easy as I still have pain but I am doing it!

Suzanne

Tymlos injections helped me tremendously. About a month after starting Tymlos my two worst pains went away. It was life changing! Months later I also started taking Strensiq and maintained the relief I found with Tymlos and experienced other improvements as well. I stopped taking Tymlos last month to see if not taking both at the same time would lesson the fatigue I was experiencing, which has worked well so far. Medicine, supplements, how much to push myself in exercise... are all trial and error with HPP.

Rebecca

The concerns we have with treatment today are:

Cost of a rare disease (multiple specialists, expensive drugs, high insurance costs) combined with an inability to hold down a full time job while caregiving for a child with HPP.

My daughter often feels like a specimen instead of a person at doctor's offices.

She receives 12 shots a week (Strensiq and growth hormone). She has lipoatrophy on both arms. Her legs and buttocks are bruised. We are running out of shot sights. As she nears the age of a teenager, I worry about those discolored and lipoatrophy areas will impact her already fragile self-confidence.

She has had 6 surgeries and has at least one more. She currently has 4 plates and 22 screws in her lower legs.

She has had multiple dental procedures and altered orthodontic procedures that extend the typical time for orthodontic apparatus.

Melanie

I said somewhat because Strensiq has helped significantly with the long bone pain and severe fatigue but it hasn't been able to fix my degenerative tendons which have developed over the last 63 years. So I am still severely limited with my mobility. I have only been on Strensiq for 3 years though.

Wendy

Since starting Strensiq 11/15/2022, my physical function is remarkably improved, but I am still significantly dysfunctional.

Lindsey

I am a patient with HPP. I am also a mom to three sons with HPP. I really appreciate this meeting as I really struggle with this disease and the other patients are validating my entire life experience, honestly. I live with severe chronic pain that greatly impacts my life. I used to always think all of my symptoms have been my fault. Even in severe pain, I am used to smiling and nodding and people around me have no idea of my severe pain, even if I am at a 10.

I would like to express that I hope there will be more education about HPP. Throughout my entire 30's I have had extensive health problems. Turns out I have 46 pages of blood work from my general practitioner - every other page low alkaline phosphatase, yet I was tested for leukemia for my low white blood cell count before HPP was considered.

I have worked very hard to get care for myself and my kids. However, the trauma I have experienced from the lack of education in the medical community is painful. Personally, about 10% of the medical community I have experienced is willing to learn and help. Otherwise 90% have said: fly to Nashville, I've heard of this but I don't have time to learn, it is ok if I get some of the letters of HPP spelled wrong, no you are incorrect of your own genetic diagnosis: you have hyposphatemia... My cousin and her son are starting to have more severe syptoms of HPP, she has tried to get diagnosed but her family care says HPP is so rare you don't have it. She's told him 5 family members are genetically diagnosed - this is genetic- still no help for her.

I have also had extreme difficulty getting help for my youngest son with HPP. He is the most severe of my 3 kids. He broke each leg before 3 years old, he has severe pain and fatigue. He wasn't able to go to school often due to pain/fatigue. His school was refusing to grant me a meeting to create a 504 plan for him. However, I am a former high school teacher (I can no longer teach due to the progression of the disease). I have a Master's in Education and am aware of the system, I had to get the director of education involved and provide his genetic report to get taken seriously. It was incredibly demoralizing. He still isn't fully understood or supported in school, but there are now some modifications in place.

I would say overall, it is incredibly challenging having everyone from neighbors to medical professionals say---- but you and your kids look normal ----- you can't have a rare disease, you can't be in that much pain, etc. Unless we are using an assistive device or limping many symptoms are invisible.

Additionally, I have kidney involvement with HPP. Kidney stones and high urine calcium. Emergency kidney stone surgeries and incredibly painful, incredibly disruptive to life and clearly I ca't care for my kids when I am hospitalized. I was on crutched with 3 fractures in my tibia for 6 months, unable to bear weight, so I was not able to cook, clean or carry my baby. This disease has dramatically reduced my quality of life.

Tracy

• 7+years of Strensiq asfotase alfa injections.These important changes occurred after the first 3-months of treatment and have remained stable.
• Before enzyme replacement my Alkaline Phosphatase level was low 17-- current blood work shows Alk Phos highly elevated to 10,000 to 3,000 range
• Before enzyme replacement Vitamin B6 very high 100. Current blood test shows Vitamin B6 within the normal range
• Micro-fractures heal quicker (ribs, feet, hands)
• Regain body strength; resume sleeping in a bed
• Prior to enzyme replacement, I “forgot” how to sneeze, cough, and belly laugh. Being a passenger in a car felt unbearably painful; we would avoid driving over railroad tracks, because the bumps hurt so much, I squealed like an animal. Eating crunchie foods jump-started the pain response. Fear of imploding from within.My ability to spend time out of the recliner was extremely limited. I was fading away otherwise pending death was rapidly closing in.Strensiq saved my life, but the pain, mobility limits, fatigue, and emotional challenges remain.
• Agree to full dentures, after incurable gum disease taxed my immune system and old teeth with previous procedures wore out.
• Medication (pain management,
• Physical therapy, massage therapy and bodywork, gentle exercise, breathwork,
• Supplements
• Foot Care (corrective shoes, custom orthotics, heel lifts, massage, warm water soaks, gentle exercise/stretching, vibrator,
• Wheelchair dependent the day a metatarsal micro-fracture sent powerful shooter pains through my body. If I tried to continue walking my heart would be in jeopardy or I would fall and break.
• Assemble an inclusive holistic team.Personal Care Assistants change ~
Birth family, husband, neighbors, friends, community, peer support groups such as Soft Bones
Old fashion pediatrician, elementary school nurses, speech therapist, physical education teachers, bone doctors, dentists, orthotic clinic, swim coach, primary care physician, endocrinologist, blood experts, pharmacist, naturopath medical doctor, physical therapist, Pain Center, Planned Parenthood, Free Clinic, rehabilitation counselor, mental health counselors, massage therapists, bodyworkers, University of AZ, local medical school, Network Chiropractor, energy healers, chair yoga instructor, learn Somatic Respiratory Integration, housekeepers, beautician, disability advocates, accessible gym & swimming pool, and more.

Karen

My daughter has had chronic neck pain since she was 3 years old. She has had orthodontia work done twice (with a herbst device). It worked at first but now her lower jaw has moved back again and she wants to have jaw surgery. Concerns about if her bones will heal correctly. She has fatigue and chronic tailbone pain. She has disordered eating and osteopenia or is orthostatic. Concerns about the only currently available treatment & side effects. Physically, mentally and emotionally draining. All of the unknowns about the disease and variants adds to that. Thank you for hosting this meeting.

Millie

How many HPP patients (I am 69 years of age) have seen reduction in height? I have lost 2 to 2 1/2" of height over the last 10 years.

Tarin

The headaches are very debilitating, unable to function without taking naproxen daily, fatigue, Strensiq has helped with this and also with brain fog. I have dental issues, have severe HPP so I am unable to walk for more than a few minutes at a time. Have pain daily, and ache, I work from home so that helps so much. Currently have a broken metatarsal which is taking time to heal so taht has been restricting, thankfully I don't have sleep issues or suffer with mental health as being diagnosed as a baby I feel I'm just use to how my life is.

Amanda

My HPP has caused severe hearing loss to where I've had to get hearing aids. I have high blood pressure and tachycardia so I worry about my heart. ADD is an issue for me along with severe fatigue and brain fog

Suzanne

One thing I think is important to mention is the shame so many of us have felt living undiagnosed with a disease which can make our brains and bodies not work as we know they should. For as long as I can remember I've thought that I am not as smart as I am. I've been so ashamed trying to hide the fact that my brain was not engaging as it should. Having a hidden disability has shaped my whole life. It's exhausting working extremely hard to be 'normal' when your body and brain just doesn't cooperate.

Wendy

The variability:

1. of symptom impact,
2. physical or mental function

Struggle to decide what is the best use of my functional time. What has to be done? Doing one task or action can diminish my abilities and choices for the rest of the day or several days.

Olivia

I am a caregiver for my mother who has HPP. One thing I want to draw attention to is the loss and grief that my mother has felt as she loses capacities. It started with her slowly losing the ability to work due to brain fog, pain and fatigue. Now its things like not being able to garden, repaint the bathroom, host a baby shower. There are lots of things that bring her joy that she struggles to do now. The other thing I'd like to draw attention to is the economic effects of living with HPP. Many people are not able to work but are still not accepted for disability benefits. My mother didn't get diagnosed until after she had to stop working. She never tried to apply for disability because at the time, she couldn't even find a doctor who would believe her, not to mention testify for her disability application. My mom was the primary income earner in our household, so this put my family in a very difficult financial situation.

Wendy

So far, my Dx:
HPP, EDS, Autoimmune Channelopathy, Dysautonomia, Mast Cell Disorder, Cognitive, and Alopecia.
My Dx journey continues: vascular, nervous system, autoimmune.

Function:
I am not able to do what I want, when I want;
But, I strive to do whatever I can, when I can.

Judith

In terms of daily life that I cannot do because of HPP - I have a very hard time doing basic chores, including doing laundry, bending to pick up items off the floor is painful, moving chairs so I can sweep/mop is painful, etc. Going grocery shopping is impossible with my quickness to fatigue, and I end up buying premade meals because of it. I use all of my energy at work, and am left with no energy or brain capacity to even focus on opening mail and paying bills. I fear that I can never be independent because of it.

Rebecca

My daughter struggles at recess and doesn't play. She just sits on the pavement waiting to go back inside. She feels "othered" in PE because she very often cannot participate in the activity. Her teacher and friends know why, but she is very aware of how different she is. She also struggles to hold things due to her joint contractors in her fingers. She drops things all the time. We have a variety of sappy cups for her at age 10 so that she can hold a handle and not drop it. She wants to play soccer but she would break and we can't let her do it.

Tracy

Prior to enzyme replacement, I “forgot” how to sneeze, cough, and belly laugh. Being a passenger in a car felt unbearably painful; we would avoid driving over railroad tracks, because the bumps hurt so much, I squealed like an animal.Eating crunchie foods jump-started the pain response. Fear of imploding from within. My ability to spend time out of the recliner was extremely limited. I was fading away otherwise pending death was rapidly closing in. Strensiq saved my life, but the pain, mobility limits, fatigue, and emotional challenges remain.

Susan

now on treatment (strensiq) has been life changings for the better for me that still isn't addressed is Scoliosis pain, have neuromuscular respiratory failure, neuropathy, and Thermoregulation I either have hyperthermia, or hypothermia in temperatures where others are just fine. There needs to be additional treatments that can deal with low ALP in other vital organs in the body besides bones.

Tracy

Born with 2 genetic mutations, Infantile & Childhood Hypophosphatasia (HPP), I offer 64-years of experience living with a rare metabolic condition. HPP affects more than bones. I experience many secondary complications: signs and symptoms in various body systems such as skeletal, muscular, nervous/brain, dental, digestive, respiratory, kidneys, and more. HPP is progressive.

Some secondary complications cause long-term trouble and others occur intermittently. My body/mind continuously changes without any known reason; new symptoms appear at any age.

Tracy’s personal list of signs, symptoms and diagnostic labels documented in chronological order within a broad timeframe. Otherwise, I’m doing pretty well considering these challenges. Note many bumps & bruises

Infancy

- Fussy/terribly upset and crying {constant attention from parents, holding, rocking, hugs}
- Translucent bones seen with X-rays {to calm a nervous mother, our pediatrician ordered my 1st X-ray at 6-weeks old to initiate the diagnostic process}
- Bowed legs
- Copper kettle skull (indentations seen with X-rays)
- Eyes protrude (hyper sensitive) {glasses at 7-years old and sun glasses}
- Projectile vomiting {replace cow milk with soy-based formula}
- Chronic pain

Childhood

- Dental issues (weak, brittle, discolored, cavities, extractions, root canals, crowns, gum infection, partial plates, finally adult dentures at 42-years old)
- Peculiar gait (leg length difference, corrective shoes, custom orthotics, physical therapy, adapted physical education)
- Scoliosis (physical therapy, back brace, beginning at 15-years old 3 major surgeries
- Speech therapy
- Slow growth (short stature)

Teenager

- Sprained, strained and swollen ankles
- Surgical procedure to stabilize severe scoliosis ~ full spinal fusion T-4 to sacrum includes halo-femoral traction with internal hardware, bed rest for 9+ months with body cast
- Physical therapy: mobility aides (cane, walking boot, walker)
- Unilateral breathing (one compressed “lazy” lung)
- Homebound education, telephone classes, visiting teacher – high school graduate 1976 with classmates.
- Ongoing dental care (fillings, root canals, crowns {gold molars}, extractions, gum disease, partial upper plate

Adult/Senior

- Ambulatory (walker/hiker from age 20 – 40’s).
- Asymmetrical body parts (skull, leg length difference, feet, scoliosis, jaw)
- Bone deformity ~ bowed legs/arms (wrist twist & feet clinch). Deformity of the iliac bones of the pelvis seen in recent skeletal survey
- Bruises happen for no reason, small black/blue discoloration marks legs/arms skin
- Chemical sensitivity
- Constipation, hemorrhoids
- Covid (August 2021) Pain issues became more intense.
- Degenerative bone at spine discs and hips (Skeletal Survey)
- Digestive troubles
- Dizzy spells, nausea, vertigo,
- Emotional ups & downs (anger, anxiety, depression, fear, joy, nervousness, worry)
- Exhaustion ~ chronic fatigue, unable to move, “hurts to relax”
- Gout (pseudo)
- Menopause (early at 46-years old, walking became difficult at 48-years old)
- Metatarsal, toe & wrist fractures (walking boot)
- Micro-fracture(s) femurs, feet (identified with X-rays)
- Migraine headaches (not recently)
- Mobility loss/impairment, balance loss, dependent upon mobility equipment for 16-years (walker 4-years & manual wheelchair 12-years)
- Muscle involvement (hypercontraction, spasms, jumpy, unreliable, unable to relax, cold, stiff, weak, shaky).“Too much contraction with not enough action” Tendons/Ligaments become stiff and bone-like, so they may snap/crackle/pop or tear, break, & stretch. Muscles take over the function bones should be doing such as protect & support the body.
- Osteoporosis/severe & Osteopenia (regular bone density examinations)
- Pain chronic (bone, nerve and muscle involvement- spasms, twitches). 2000 to current– electric shocks/jolts, muscles contract for no reason, stab felt in heels, buzzy & puffy ankles, toes cut-off, feet like cement, exhaustion, weakness, “My feet rule”
- Peripheral Neuropathy (buzzing, cold, numb, extra-sensitive legs/feet/skin)
- Physical therapy: mobility aides (cane, walking boot, walker, treadmill, pool fitness, massage therapy)

• Ribs – recent skeletal survey shows multiple bilateral healed rib fractures. Ribs fractured since beginning Strensiq, so the fact they healed in the past 2+ years is good news.
• Shingles (skin rash, redness, itchy)
• Sleep difficulties-- sleep myoclonus/ hypnic jerk, insomnia (gradually core strength vanished; 2015 a recliner chair became necessary for naps and night-time sleep. Today, I sleep horizontality in a bed. Strensiq helps regain strength.
• Stones (gallbladder)
• Stress
• Sudden Hearing Loss (March 2022)
• Tinnitus (ringing in one/both ears)
• Urinary Tract & Vaginal Infections {diet, hygiene, antibiotics}

• Alkaline Phosphatase = low 17 and Vitamin B6 = very high 100 before enzyme replacement treatment. After 7-years of Strensiq injections, current blood work shows alkaline phosphatase = 6,000 and Vitamin B6 decreased to normal range. This important change occurred after the first 3-months of treatment and has remained stable.

Judith

I had to drop out of college due to severe brain fog, ADHD and excessive fatigue/sleep. I've seen over 5 different neurologists and been tested multiple times for narcolepsy due to the severity of symptoms. After being dismissed multiple times and accused of faking/lying, I was given a generic "idiopathic hypersomnia" diagnosis and with the help of stimulant medications, was finally able to graduate with my Doctor of Pharmacy degree. There's a question now about if HPP is the true reason for these "unusually presenting" symptoms since I only got that HPP diagnosis recently, but they remain so significant that I can barely work a full time job enough to ensure I keep the health insurance to cover all of my medical appointments, tests, and medications. But now with the HPP diagnosis, if we are able to improve that aspect of my life, I could finally have my life back!

Mike

Curious about the number of patients taking Strensiq and the symptoms most reduced by the treatment

Wendy

Thank You Lindsey!!!

Dysautonomia!

Co-morbities!

Let's talk about all of it!

Suzanne

My sister describes the difficulty of talking to doctors about the pain of HPP. She says, "It's like I have 27 thumbtacks in my foot and am asked to talk about just one of them. There are so many kinds of pain. Muscle pain, bone pain, joint pain, overall pain.... To me it is like the painting, "The Scream." So much pain it's overwhelming. Treating it with pain meds is just chasing it. Nothing works. It ends up chasing you. You can't get away from it.

Louise

The fear that your child will die before you, even on Asfotase Alfa which has been great with her long bone. but to see she has less mobility each year because of pain in her joint still needs to be address. A person with two mutation needs more treatment than just fix the fractures in order to have a quality of live as she becomes a older adult. I see isolation
becoming her normal because of pain of the joints. even seeing her giving up things she loves like paining and sewing because her finger range of motion is getting chronic pain.

Tracy

Prior to enzyme replacement, I “forgot” how to sneeze, cough, and belly laugh. Being a passenger in a car felt unbearably painful; we would avoid driving over railroad tracks, because the bumps hurt so much, I squealed like an animal.Eating crunchie foods jump-started the pain response. Fear of imploding from within. My ability to spend time out of the recliner was extremely limited. I was fading away otherwise pending death was rapidly closing in. Strensiq saved my life, but the pain, mobility limits, fatigue, and emotional challenges remain.

Tracy

Historically, compromised HPP bones show-up as the most concerning healthcare issue. Please accept the fact HPP not only effects the skeletal structure/function. Each body/mind system deserves attention if someone is diagnosed with HPP: muscles, tendons, ligaments, nervous, respiratory, circulatory, digestive, excretory, etc. Muscle structure & function compensates for deformed/weak/brittle bones by becoming extra flexible and/or way too tightly contracted/fused.

The HPP nervous system over reacts to sudden stimulation by sending intense messages throughout the entire body to warn of possible impending danger/doom. These jolts/spasms/lightning bolts start the pain response because of a rare anatomical and physiological combination.

Wendy

Hello,

I am interested in participating as a voice/advocate, clinical trials, genetic data studies, and any other ways that can aid with medical advancement and patient support but have been hesitant due to my highly variable levels of functionality both physically & cognitively.

I feel it takes all my energy, strength, and moments of function trying to manage my Healthcare, maintain and improve physical function, navigating variable symptoms, and trying to optimize every day.

Despite all the challenges, I feel extremely fortunate, there is so much to be thankful for and I believe I will gain more functionality.

Ashley

As a wife of an HPP patient who works as a firefighter/paramedic, in this phase of life, I am most concerned about my husband's ability to work which is currently our only source of income. I would say his biggest concern relates to his role in our family and concerns he won't be a good father because he's anxious about participating in their lives as they grow up. In a rare moment, he was brutally honest about his concerns about being a "burden" on our family. I was heartbroken.

Many people don't think anything is "wrong" with my husband but like many HPP patients, he has learned to mask his physical ailments and decides to just get on with the day. He had resigned himself to silently suffering until Strensiq was finally available to him. It's not a cure for him but we now know there's finally a treatment.

I was fearful when we started discussing our own family because there was and still is a lot of unknown about this disease. My greatest fear was we would experience the joy and elation of pregnancy only to have it end tragically in a loss. I wanted to know what quality of life a potential child would have. So many questions rooted in fear that we had to contemplate. We were fortunate enough to have a discussion with a geneticist who was informed.

We have two children under 6 right now and they've both inherited one mutation each. It's been a big concern about how their bodies will be affected as they grow, and we are monitoring them as best as we can.

Stephen

I'm attending as the dad of two adult kids - female ages 28 and 26 - with HPP. We are on the lower end of impact but still are affected by HPP. Neither could attend because of work. My wife also cannot attend due to work. I'm multitasking ... just an observation about the time challenge for attending which may have skewed the age results of your survey.

We were part of the Shriners research program with Dr. Whyte. Both girls are in their "good years," but still have multiple issues. They aggressively manage their lives to minimize the impact ofHPP. We have not been involved in any drug therapy programs. Thanks for doing this -- ST

Laura

Symptoms that have the most impact on daily living are:
1) extreme fatigue
2) brain fog/inability to focus whether on work or people
3) pain/discomfort of bones, tendons, and muscles

Ellen

As I aged, my joins and spine causes me to discountuned activities because of the CPPD growth, and pain.

Donna-Leigh

I have had to drastically reduce what was an active life. I have the type of HPP that goes dormant in young adulthood. I was able to work out almost daily. I could squat over 100 pounds. Now it's all I can do to walk around the block. Getting an appointment with a doctor with any knowledge is very difficult. I should be able to work more than I can. Now when I do work I am exhausted and just need to crash. The fact that the paperwork required to get Strensiq is so complicated makes many doctors not want to even mess with it. It's all very exhausting.

Millie

The most significant impact is eating. It takes a very long time to chew and swallow food. Then, I am always on guard for my teeth crowns to dislodge. So far I have not swallowed a crown, but chew cautiously for a hard piece of ceramic or gold crown. My mouth and eyes are extremely dry.

Melanie

What symptoms of HPP are the most bothersome?
Gnawing bone pain which moves around the body. It can be in multiple places at once and from severe to excruciating. There is a never a day without pain. Pain from chrondocalcinosis, tendinopathy, headaches and degenerative tendons are my experience. I have had one non-traumatic hairline fracture in my femur.There is no day without pain.On top of this there is severe exhaustion and brain fog. Muscle weakness and pains in the muscles. Mental health issues in trying to continue dealing with the constant battle to see specialists and very limited help to manage your journey with HPP. The only medications readily available are pain killers and antidepressants if you are not able to access Asfotase Alfa.

How does HPP impact activities of daily life?
There is exhaustion just dealing with everyday life and the symptoms of HPP. If you add in school or working on top of the pain it is hugely difficult to cope day in and day out.
Making journeys unsupported difficult both with driving and mentally and travelling alone is extremely difficult as we really struggle to carry or pull luggage.

Kitchen:
I find using an oven difficult due to lifting things in and out of the oven.
I find the whole process of cooking and preparing exhausting as it causes severe pain in my hands, elbows shoulders and feet if I need to stand for any length of time. I have severe pain when chopping, peeling, opening lids, cans or even lifting items down from shelves. I find gripping anything or to lift or chop causes severe shooting pains down my arms. If I am left home alone I would eat cereals as it is easy to prepare or choose something easy from theI am freezer. The problems I have are continuous throughout the day.Consequently my husband always cooks and I go and stay with one of my daughters if he is away for any length of time.

Eating:
When eating I have great difficulty cutting my food due to severe pains in my shoulders, arms, elbows and hands. I always have pain when raising my food to my mouth and when lifting even a mug. To try and help with the situation I have a small china cup and steak knives fitted with push-fit handles. My husband will often cut up my food for me.

Washing/Dressing:
I am unable to get out of our bath due to muscle weakness and pain so we have had our bathroom changed and put in a large shower with a stool to sit on. My husband will have opened the shampoo and conditioner for me or I purchase pump action products or transfer them. I have difficulty washing my back and therefore have a long handled brush but this gets more and more difficult to use due to the problems with my shoulders and arms. I struggle to wash my hair and on some days my husband will do it for me. I have a grab rail fitted.When I am in unbearable pain I will decide not to have a shower on that day. I use a bathrobe to dry myself and will sit in bed for a while to dry off. My husband cuts my toe nails for me as I am unable to do it due to pain and weakness in my hands.
Drying my hair is extremely difficult and painful. I have bought a wire support to hold the hair drier together with a very light weight brush. My husband will sometimes dry my hair for me but I find this very upsetting as I wish to do my own grooming.
Due to muscle weakness and tendinopathy which causes severe pain I find it extremely difficult to put on and take off jumpers, vests, bras, t-shirts etc., My husband assists me with dressing and undressing. He will help me take off my trousers and my shoes of an evening too.
If I had to dress on my own I would not wear a bra and I would wear shirts and cardigans that are a little easier to put on. I would wear loose fitting trousers that are easy to pull up and take down. I have slip on shoes that I can wear around the house. I also have a dressing gown which I can wear over my pyjamas if necessary.
I find dressing causes tiredness and I have to choose my clothes according to my pain levels on the day. Pain is always worse following dressing. I tend to wear trousers most of the time as putting on tights is impossible. I find it takes me at least three times as long as my husband to shower, dry and feel presentable.

Working:
Having a disability doesn't take away your wish to work and be a valued part of society but being able to do this is extremely difficult. My experience was it was very difficult to declare my limitations and receive the adaptations or adjustments required to do the job because on the whole I look OK.Eventually I gave up trying and became self employed in order that I could pace myself and buy the equipment I needed to do the work.

Socialising:
Every day has to be planned in order to be able to make the most of every day. It is very difficult to be spontaneous when you are in constant pain and even more difficult to be sociable. So each day you make choices and prioritise so that you can achieve your goal. Very often people don't understand your reluctance to take part in activities even though you try to explain time and again. The difficulty is finding a balance as you still wish to be part of your circle of friends and do 'stuff' but not make them feel guilty for excluding you or making adjustments.

Sleeping:
It is often difficult to get to sleep due to the pain. You are easily woken up because you are often just dozing. When you do sleep you then can barely move when you awake because you become extremely stiff. Getting out of bed in the morning is extremely difficult and it is very hard to take the first steps. Your muscles tend to seize up and there is severe pain when trying to move.

What have you done to treat or manage HPP? Has it helped?
I have had numerous operations: on my back and on my shoulders and countless cortisone injections all over my body. When the condition becomes so severe in one part of the body that you need an operation this is your only option. Unfortunately you then still have to deal with the operation plus the other severe pain in your body. It is a vicious cycle and very traumatic to deal with time after time. There are times when you have had enough and mentally it is a huge fight to continue.
I have paid privately for osteopathy, podiatrists, physiotherapy, acupuncture, reiki, Bowen technique, aromatherapy, massage, mindfulness course, hydrotherapy and shockwave therapy.Unfortunately there is often a long wait for much needed surgery and you end up having to have something to keep you going through these tough months when all you can do is sit with heat pads and do nothing. At least by visiting alternative options as above you can try and keep hopeful and focussed.
I have been lucky enough to access Asfotase Alfa in the UK under the Managed Access Agreement which is now under review. My life has changed completely since being on the medication.
I feel that Strensiq has halted the progress of the disease over the three years I have been on the drug. It hasn't removed all pain as it can't repair years of damage done prior to the medication but I have hope for the future and feel better able to cope.
During the period on Strensiq I have not had to visit my GP for HPP. My pain medication usage has reduced significantly. My anxiety and depression has also improved also due to reduced pain and because I have hope that the medication will stop me breaking bones and developing other complications - my medication for depression is reduced by two thirds!
There is nothing else out there as far as drugs are concerned that can equal the efficacy of Strensiq at the present time. Even though the drug is painful to inject that is insignificant when compared to the reduction in pain, fatigue and depression.

For the 7 years prior to starting on Asfotase Alfa I saw 50 different consultants, had 4 operations and heavily relied upon opioids, NSAIDs, antidepressants and cortisone injections.During this time I have lost count of the number of visits to my GP and physiotherapists. Since being on Asfotase Alfa over the last 3 years I have only needed to visit my consultant for monitoring purposes as she is reviewing my progress for the MAA! This evidence is compelling and life changing!

What are your hopes and desires for new therapies? i.e. what symptoms do you want to see addressed?
My hopes for new therapies are that all patients living with HPP with symptoms that effect their qualitity of life would be able to access a treatment that would help manage the pain, exhaustion and stop the progress of this unrelentless disease no matter the age of onset of symptoms. I feel the present definitions of perinatal, infantile, juvenile and adult are obsolete. It is only over the past 20 years that clinicians have been learning about the condition and as patients we are still training our doctors on how it is to live with these symptoms. It is still very difficult to find a hospital with knowledge of HPP and it is also a fight to get referred to someone who does know about the condition.Many clinicians are still giving a diagnosis according to how old you are when diagnosed. Therefore there are many patients who are put into the wrong category and are then unable to access Asfotase Alfa.

How much risk would you accept for a given therapeutic improvement?
As mentioned above there comes a point in life when you can't face any more invasive surgery or cope with the pain any more. So I would accept there may be side effects but if it would improve my quality of life I would be prepared to try new therapeutic forms.

Ed

HPP symptoms that most "bother" me....the constant, unrelenting pain that is not treatable in my country for reasons unknown. Why is strensiq not available for those of us that are suffering?????

The impact on my life? Had to stop working as it's impossible to go to work in the physical condition this disease puts us in. Some less, some more. This also affects our families who rely on us to be the earners and now cannot. Why is strensiq not available in our country? It has been proven effective. Why is this not available in my country????

Adam

Worst symptoms: pain and fatigue

Richard

I submitted comments yesterday on behalf of my son Mike but would like to add the following:
I have described Mike's physical symptoms and his medical journey, but let me address his quality of life. When he was on Strensiq he had not improved enough to hold a job but he was able to volunteer at an animal shelter on days when his symptoms were relatively better. That stopped late in 2021 as his symptoms worsened and expanded. Since that time his pain and fatigue make it difficult for him to be mobile, his brain fog makes it impossible to drive himself anywhere or do the things he loves the most, reading and playing piano and guitar. He reads some when symptoms allow, but playing music has been out of the question since early 2022. Mike only leaves the house for doctor appointments and we drive him. The vibration of car rides bother his newly developed sensory sensitivity to light, sound, vibration and touch. Needless to say he has no social life except for interaction with Nancy and I. He fights depression and anxiety on a daily basis, some days better or worse than others. Longer car rides, such as our trips to Cleveland Clinic, exhaust him and often make him nauseous. He hasn't been to Nashville to see Dr. Dahir since May 2021 because travel is so tough on him. Our 3 1/2 hour car rides to Cleveland Clinic leave him spent for days afterward. Mike is an intelligent guy with a graduate degree from Columbia University, yet he has been reduced to watching movies or listening to soft music in his room, every day. His quality of life has long been negatively impacted by HPP, both in terms of the quality of his activities and the limits to his activities. More recently with his expanded and more severe symptoms, his quality of life has been reduced to the level of a shut-in sick person. Obviously this negative progression has had a major impact on Nancy and I. We no longer feel comfortable leaving Mike for vacations, nor is he able to come with us. We rarely go out to dinner and we have been afraid that whatever disease he has beyond HPP make render him immune compromised, so with Covid in mind we avoid social situations. Needless his condition has had a profound impact on all of us. Thank you. Rich Hanlon

Debbie

- Muscle weakness/muscle fatigue
- GI upset along with syncope … one preludes the other …chicken or the egg theory
- Bladder pain(since I was a child urinary track infections , now interstitial cystitis, which I believe wholeheartedly comes from excreting excess B6)

Outside of health issues because there are too many on the list, I cannot hold my job anymore.
And the worst part is when you are then treated unfair/or rather DENIED TREATMENT/CARE from a worker injury, at a hospital that you gave your last ripped tendon and ligament to after 32 years, and saved countless lives…

When I told the treating physician at my job that I have a rare disease called hypophosphatasia and maybe this is why my back injury, my torn tendons are not healing.
She said, “there’s nothing functionally wrong with you. You can go back to work.!!!!

I don’t know how some people can put their heads on the pillow at night. This MD should be fired or sued at the least.

Biggest name hospital in our country too…….disgusting!!!!!

Isaac

I experience major fatigue, major inflammation, major food allergies and major brain fog to the point that it's difficult remembering things, I'm probably forgetting some but that's me. I don't have and have not experienced brittle bones or teeth, I'm very thankful for that but it seems there are a lot of other symptoms that everybody talks about in the HPP community that are never addressed or it doesn't seem like it. I'm on Strensiq and I have noticed a difference but a lot of up's and downs and I don't know why, I can only guess it's because of all the other things I'm dealing with causing the issues. Thanks.

Richard

Hi my name is Richard Hanlon, I am a co-caregiver and father of HPP patient MIke Hanlon. MIke was diagnosed with HPP in 2017 at age 28, after 10 frustrating years of doctors and surgeries with no explanation of his symptoms, i.e. joint pain, fatigue, brain fog and sleep disruption. Mike was forced to stop working in late 2016 because of his symptoms and moved in with my wife Nancy and I. Mike did not have classic soft bones leading to fractures, instead he had reoccurring bone spurs/chondrocalcinosis in his big toes and hips. He suffered four foot surgeries before he was diagnosed, all which failed to resolve his bone spurs, which would reoccur after the surgery. His last foot surgery was a big toe fusion, which failed to fuse. Little did we know his undiagnosed HPP would not allow his fusion to mineralize. His toe was 90% soft "fused" on x-ray when it suddenly stopped, reversed and disappeared. The doctors were perplexed. The soft fusion couldn't mineralize because of his HPP, but we did not know he had HPP. His body simple reabsorbed the soft fusion. Mike was tentatively diagnosed with HPP in late 2016 after extensive testing at Cleveland Clinic for autoimmune diseases (which is what we suspected he had) and confirmed in early 2017. The endocrinologist that confirmed his diagnosis at Henry Ford Medical Center had little experience with adult patients and thus little familiarity with the nuances of the disease. Mike eventually found his way to Dr.Kathryn Dahir at Vanderbilt University Medical Center. Dr. Dahir has one of the largest adult HPP patient cohorts, which is very important for understanding patient experience with a highly variable disease such as HPP. Dr. Dahir further diagnosed Mike's ALPL variant, a rather uncommon dominant ALPL gene variant, c.1364 G>A, p. Gly455Asp. Mike started asfotase alfa (Strensiq@) enzyme replacement therapy in October 2017 once he was able to demonstrate childhood onset (e.g. low ALP, scoliosis, reoccurring leg pain chalked up to "growing pains"). Unfortunately Strensiq was not a game changer for him - he saw some modest improvement but continued with all his symptoms, albeit in a somewhat improved version. Early on he began to develop injection site reactions in his stomach, hard sub-surface "knots", lipohypertrophy. He carefully moved his injections around, but to no avail. He also tried different needles as well as different injection schedules - first two injections three times a week, then one injection six times a week. He also tried his thighs as well as under his upper arms. Injecting in these places was very painful - he is lean with little fatty tissue to absorb the medication. Nothing seemed to help his injection difficulties and his injection site reactions continued to worsen - his stomach bulged with hard knots that made it look like he had swallowed a bag of unshelled walnuts. His symptoms also eventually started to worsen and Dr. Dahir believed that the subsurface reactions had begun to limit his uptake of the Strensiq.

His injections were painful and the benefit seemed to be waining. In October 2020, after three years on Strensiq, Dr. Dahir and MIke agreed to stop his treatment as it was apparent it was no longer providing benefit. About six months after Mike stopped the injections, his symptoms began to worsen and expand. In addition to his previous symptoms of joint pain, sleep disruption and brain fog, he developed painful skin rashes from sun exposure as well as hot showers, bouts of nausea and dizziness especially after showers, and night sweats. He also had abnormally high red blood cell and hemoglobin counts. In early 2022 he began an intensive hematology evaluation, and saw a local hematologist, a University of Michigan hematologist, a Memorial Sloan Kettering hematologist and a Cleveland Clinic hematologist. Despite having symptoms that suggested a myeloproliferative neoplasm cancer (blood/bone marrow cancers), none of the hematologists were able to identify any of the many genetic variants associated with such cancers and it was concluded he did not have cancer. Mike subsequently has seen a battery of specialists at Cleveland Clinic - neurology, dermatology, pain management, sleep disorders, endocrinology, rheumatology, genetics and allergy/immunology. He has been tentatively diagnosed with fibromyalgia, but no other primary disease, to his and our frustration. His doctors believe that something else besides HPP is going on with Mike, we just haven't found it yet, it hasn't presented itself with diagnostic markers yet. His symptoms have continued to gradually worsen and for months he has self-confined to his room. Judging from comments of other patients on the SoftBones patient/caregiver portal, many have multiple diseases. One might conclude that HPP is a "gateway" disease that opens the door for other diseases. Mike's medical journey and suffering continues as he seeks answers that explain symptoms that do not seem to just fit HPP.
In the meantime, HPP patients need a treatment that: 1) works for all ALPL variants, and: 2) does not produce injection site reactions. Thank you.

Gretchen

I am mildly affected and just recently formally diagnosed. My life has been impacted in a lot of ways. After a small fortune spent on dental work and hundreds of hours spent in dental chairs over my lifetime I will still lose my teeth. At least now I know why. After being depressed since I was a child at least now I know why. After mysterious bone bruises in both knees have hampered attempts to stay active and lose weight, and neuropathy, carpal tunnel, tendonitis and hip pain wakes me up nightly. At least now I know why.I endure the pain the best I can, avoiding nsaids because of the risk of organ damage with long term use. I may have nearly killed a 18 year old beloved pet by using topical nsaids.My symptoms are mild enough to not warrant Strensiq. (We shall see what the future holds). All but one of my doctors think I’m a hypochondriac and dismiss my concerns about HPP as being a made up thing. So for now I say ow a lot and some other things I won’t share here.

Millie

My most frustrating part of HPP is the damage done to my teeth. My four bottom center teeth have not been crowned as of November 2022. All my other teeth have been crowned, some older ones with replacement crowns. My extremely dry mouth causes the crowns to come off and they are recemented by dentists. The other aspect is having to eat slowly in order to swallow bites and are supplemented with drinking/swallowing lots of water.The ability to pronounce words is difficult when my tongue and the roof of my mouth get too dry to say a word with three or more syllables. My teeth are brittle, and I have worn off the enamel.

June

What time is it this Australia eastern daylight saving time

Breeanna

My son was diagnosed with HPP when he was 2 months old, we have been on it since and he is currently 8 months old. Something that we noticed has been an ongoing issue his weak swallow. He's been told by several speech therapist that the way he sucks his pacifier is abnormal and his technique almost seems compensated for the lack of muscles he has in his throat area. We have done two swallow studies (one at 2 months and one at 8 months) and both studies showed that his lack of wanting to eat is because it there is struggle with him getting his throats squeeze the food down in one motion and not through a series of motion. Liam also has hyper mobility. Because of this, physical development has been quite the work. Currently he will asleep with his feet being, in what seems to be, very uncomfortable positions. He wants to stay in the middle splits constantly and struggles getting to the crawling position. Instead he'll be the frog position wanted to move but struggling to figure out how to get his body to act accordingly. Our concern is as he continues to grow, this may lead to serious hip problems. And delay in standing/walking due to lack of muscle strength. Most of our PT hang ups are not that he isn't wanting it but more of his body is not strong enough to get there or he has learned a different way to get to that same goal, but that way needs to be correct because it will eventually lead him to struggle in other growth development.

Despite these issues, strensiq has been a blessing for our family and we do see benefits for Liam since he's started taking it, and we are optimistic to see how modern medicine can help him live his life to the fullest.

Stephanie

Does Hpp cause calcium buildup in the brain? If yes,might we view this as a reversible cause of dementia? (I am 59 and figured out the diagnosis a year ago. My Mom,her Mom and five sisters experienced cognitive issues.) Thanks

Sheila

My most bothersome symptoms have been systemic and soft tissue related rather than fractures. I have had many soft tissue injuries, full body pain, extreme fatigue, severe neurological symptoms such as confusion and anxiety, and problems with my teeth leading to root canals and implants due to bone loss. Strensiq has helped immensely with all of these. I would like to see a new therapy that didn't require injection - the site reactions are ruining my skin and the sagging skin is getting uncomfortable. One quality of line issue is that I'd like a drug that didn't require refrigeration so that I could travel more easily.

Jessica

The most common HPP symptom in our home is sub-par connective tissue.. so issues with things moving where they shouldn't (causing pain then as well), eye problems, lung problems, gastrointestinal problems. The second is fatigue. The bone issue is third.
This is not a 'bone disease' so much as a systemic metabolic disease which affects connective tissue...in our home at least.

Jennifer

As a patient living with HPP, and one diagnosed very late in life, I can vouch that the bone pain is excruciating.The fact that I have a bleeding disorder too, prohibits me from taking aspirin or NSAIDS to assist in managing that pain. Additionally, my joints are weak, and it seems, my ligaments and tendons are even weaker. They tear too easily. I have already had 22 surgeries and have broken more than 40 bones thus far. I have at least 3 more surgeries in the offing.

It's sad that no one knew about this disorder even though I asked each orthopedist (and there were so many) why this kept happening and each time, the blame was put on me. Having received no real answer, I had children. I ended up with three children, but had 6 pregnancies. The miscarriages were devastating. Regrettably, all three of my girls have HPP too. Between the four of us, the trips for medical intervention is never-ending.

Strensiq helps with the pain and other issues like brain fog, but 6 injections per week takes it toll. And the injection sites get overused and the sting of the injection is ever-present.
A once a week injection would be preferable or some sort of an oral medication would also be welcomed.

I would not want to live life without something that mitigates at least some of the symptoms of HPP, but we would appreciate a better alternative.

Jessica

When our daughter was born, our lives were turned upside down. We had no idea about HPP and that we BOTH carried it and our daughter inherited both bad genes. She was born, as I like to say, with toothpick like bones. So little of bone, they were not sure if she had certain bones to begin with. Immediately intubated and flown to a childrens hospital 2 hours away from home. We had no idea the outcome of her and watching her fight day after day. By god a dr that day she came in saw, her X-rays and knew right away she had HPP and got her started at just two days old, on Strensiq. If it weren't for this medication, our daughter would not be with us. Almost two years later, we are getting somewhere. Being she's two, she still is not walking. She is learning to stand more and more these days, but we are now noticing her feet cave inward. This will be a challenge in itself. But let's not forget about the bowing in ALL of her limps. The hyperextending of all limbs can affect daily life. She's not old enough to tell us much, but my experience with HPP, I have good days and bad days. There's days where I can't sit nor stand for 30 mins at a time or I am in sheer pain. My heart breaks for my daughter being that she's double affected by HPP. We are forever grateful for Strensiq and hope one day they can possibly get a different form on medication.

Or once a week versus 3 times a week. As much as we love our daughter and will do anything for her, it breaks our hearts every Tuesday Thursday and Saturday having to pull up the medication and poke her yet again. She has gotten much better, but she carry's so much medical trauma/anxiety with her that when we wipe her with the alcohol prep pad, she is already panicking. It used to be worse, and we could not put lotion on her body without her screaming in fear. We hope one day technology will further advance the medication for all HPP'ers.

Nicole

Several birth defects have been found in me including heart shaped uterus, Azygos Lung Lobe, deviated septum, heart murmur with atrial & mitral valve regurgitation causing supraventricular beat, and Brachyldactyly Type D. This has caused reproductive issues, high heart rates, and chronic sinus infections.I have to use s CPAP. Ive developed scoliosis and bulging discs causing back pain and migraines. I have toxic Vit B6 levels causing migraines, mental health issues and neuropathy. I get joint pain. I get fatigue & weakness. I can no longer ride a bike linger than 15 minutes. I can no longer crochet longer than 10 minutes. I cant hike over 20 minutes to 30 minutes. I have difficulty getting chores done. I can only work 8 hrs a week. Im trying to get disability.

Kathryn

What symptoms of HPP are the most bothersome? I have daily joint pain in my knees, hand, wrists, and shoulders to name the worst.
How does HPP impact activities of daily life? I'm only 36 years old and can't run with my child, sit on the floor and play with my child. General excessive is hard to do.
What have you done to treat or manage HPP?I started Cymbalta. Has it helped? It has helped lower my pain level. I can gently jog now.
What are your hopes and desires for new therapies? i.e. what symptoms do you want to see addressed? I'd like to see more pain management for those of us with less severe HPP.
How much risk would you accept for a given therapeutic improvement? I would accept some mild risk.

Pernille

Hi,I have the childhood form of HPP, which was diagnosed early on as I had troubles learning to walk and also lost many of my baby teeth early on. I'm now 35 ya.

Since I had my son at 28 and after turning 30 I feel like there's has been a shift in how severe my HPP symptoms are:
1) My pain experience has gotten worse. I manage it by only working 5 hours/week and doing exercises 2-3 times a week guided by a physiotherapist. 2 of those times in water, where 1 is in a warm water pool. I spend a lot of energy taking good care of myself, eating well, resting and working out, because I have found no other medicine or treatment. I have a lot of diffuse pain with no explanation when looking at x-rays or when looked at by doctors and my physiotherapist.

2) For more than a year I've had several stress factures in my right foot. 4 of which have healed, but the last major one is not healing. I get x-rays of both feet every 3rd month to check for changes in the feet. There has also been signs of beginning fractures in the left foot. If my right foot won't heal we're considering surgery to stabilize the foot and bones, but I'm very hesitant, since I have a history of not healing very well, and I fear that the screws will cause troubles. I'm soon out of options though.

3) Worst of all is that I have started to get pain in my hands and arms. Mainly in my right hand, which is my writing hand. We can't quite figure out what causes the pain, wether it be osteoarthritis or something with the tendons. I know at some point I might not be able to walk on my own anymore, but I never thought that I would get trouble using my hands. I'm an illustrator and all my passions and hobbies are something with my hands. I used to play music (piano and guitar), I used to knit, and I used to always keep busy with my hands, but now I can't. When I can't walk and I can't use my hands, then I don't really know what to do with myself anymore. There's not really any recognition in my country of the wide aspect of HPP symptoms, so I'm very much on my own with these questions and this fight.

4) I've struggled with symptoms of depression and insomnia for as long as I can remember. Since I have begun using Melatonin my sleep has gotten much better. I mention this as something related to HPP, because I've heard that the low level of B6 in the brain could be related.
My wish is that there will be some kind of treatment available for patients with HPP - not only in US, but also the rest of the world. I wish that the medical cost will be at a level that we all can afford. I'm not sure what's causing the pain in my hands - perhaps the elevated level of B6? Or the low level of ALP? But I've heard that Strensiq will improve both, and I feel optimistic that it could help my situation, both in terms of bone healing and other pains.
I wish that treatment will be available not only to children, but also to adults with HPP.

I'm willing to take a great deal of risk when trying out new medicine. But as long as I have a child living home, I also need to be healthy enough to take care of him - so there's a limit still. Otherwise I would gamble it all if there was a chance to eg get my ability to use my hands freely back. Or how about taking a walk? That would be something.

Thank you for your time.
Best regards,
Pernille Blaabjerg Mathiasen

Laura

With new treatments being developed, especially as HPP gets recognized earlier and earlier, what can be done with new treatment they wouldn’t require constant refrigeration? This makes it very hard to go on vacation, travel internationally or even just go camping for a few days. The current treatment actually places limits, while helping at the same time.

Amanda

My HPP affects my hearing, my teeth, my heart, my bone structure, joints, and fatigue. I have hearing aids for my hearing loss. I tried to get braces to correct my teeth but my dentist had to stop the dental work due to vast bone loss. I have to take bata blockers for my tachycardia. I have anxiety and depression. The worst part of HPP for me is the fatigue. I also worry about my heart giving up on me.

Alison

I was diagnosed as an adult but had symptoms as an infant before 2 yrs old - went to doc weekly bc wasn't growing / failure to thrive. Finally starting growing more after mom stopped breast feeding me at 2 yrs old - now understand body wasn't metabolizing calcium properly.

8 years ago was having extreme fatigue and brain fog. Went to many docs, was dismissed even though the low out of range ALP was right there in my bloodwork. Took gluten out of my diet and that helped for little while.
In 2021, went back to doc for fatigue and brain fog, hard to concentrate and articulate communication. Finally was sent to an Endo who diagnosed me with HPP.

My most bothersome symptoms are the fatigue, brain fog and hard to concentrate. It's hard when you're in business meetings with elite people and you can see the words but have a tough time putting them together and sounding articulate. Would love to see more research on the neurological effects for adults and over time. I'm currently on Strensiq and it is helping with fatigue and being able to focus and be more clear in thinking.

Would love to also understand long term effects of Strensiq on adults.
In future, would love if there was a pill format or other. The injections are so painful.

Sandy

1. Joints, tendons, ligaments, muscles, achy bones.
2. I have to be on hard level surface to walk, if I'm not I take smaller steps, and need to hold onto something if available. Stability issues.
3. On Strensiq, hydroxychloroquine, Tylenol, and Celecoxib. Starting to move up and down steps easier after being on Strensiq for 6 months.Hydroxychloroquine to help with inflammation, Tylenol and Celecoxib for pain. Still in pain some days less than others. Some days I puff up with inflammation.
4. What I hope to see, having not to stick myself with needles 3 times a week.Walking issues and better pain management.
5. Risk I would be about a 6.

Abby

I am a 71 year old woman diagnosed with HPP in August of 2022, so only 2 months ago, although obviously I have had this illness for years, breaking 10 bones within the last 10 years, including both of my femurs. Both siblings are currently undergoing testing, and I suspect at least one of them has it. Despite years of low alkaline phosphatase, no one ever even considered a diagnosis of HPP until I went to the Yale University Bone Center. I suspect I am far from alone in the quest for a diagnosis.

The symptoms that cause me the greatest difficulty are, of course, the frequent broken bones and the random intermittent joint and muscle pain. I have significant difficulty going up and down stairs, cannot stand for any period of time, cannot walk for long depending upon the surface, have difficulty with my grip, and struggle with headaches and fatigue. I also experience significant sleep difficulties because of pain and awaken roughly every 1.5 hours throughout the night.I am currently in PT for gait and balance issues to improve mobility and stability, which may prove helpful.

These symptoms, which have worsened in the last 2 years, mean I no longer shop for groceries, or much of anything else.I am no longer able to clean the house, or, if I do, cannot then do anything else for the rest of the day, and possibly the day after. I am capable of unassisted self care, fortunately, and can still manage things like laundry and dishes, but I do not cook because it requires too much standing.

I have taken all of the standard anti-inflammatories, and now take meloxicam and plaquenil, both of which are probably helpful, but not enough to allow me to do more. I am also now taking gabapentin, but at the lowest dose with rather limited efficacy. I have yet to titrate up because of negative side-effects. It appears as if I have been approved for Strensiq, but have yet to start treatment so I do not know if that will offer any symptom relief.

From my perspective, what is most important in treatments are the prevention of additional broken bones, mobility issues and pain management treatments that do not involve opioids.At my age, I am probably not inclined to assume a significant risk or negative side effect profile in trying new treatments. But that is just me. I have lived a long time with this disorder without ever knowing what I had, which probably affects my perspective somewhat. It has gotten worse over time, but it is all I have ever really known.

Taylor

What symptoms of HPP are the most bothersome?

- Extremely debilitating fatigue, muscle weakness and pain, headaches (daily).

How does HPP impact activities of daily life?

- It impacts every aspect of my day.

I have to plan around my fatigue. I can only walk short distances. I can’t lift anything heavy. So groceries and products must be delivered, shopping online as I’m too tired to go in person. Emotionally this is exhausting. It causes anxiety and depression because of the restrictions and always trying to plan ahead but never really being able to.

What have you done to treat or manage HPP? Has it helped?
Strensiq- took the edge off . No more bone pain but severe muscle pain and exhaustion is still as present

What are your hopes and desires for new therapies? i.e. what symptoms do you want to see addressed?
Anything to help with tiredness and to help the muscles have energy and strength

How much risk would you accept for a given therapeutic improvement?
Pretty high. Almost anything

Emily

The most troubling symptom for me was weakened bones. I was a high level athlete until I started fracturing. The most important thing for me is rebuilding bone. I had to quit my sport, and it was devastating. I was on strensiq for 1.5 years, but my condition worsened significantly. I developed many new symptoms consistent with an autoimmune disorder, buy my doctors couldn't find a diagnosis. I also lost significantly more bone after a year and a half on strensiq. I stopped taking strensiq at that point. Within a year, my autoimmune symptoms stopped, and I regained a little bit of bone density. I think that my body reacted negatively to strensiq because I feel so much better without it. For new therapies, something that's not an injection would be amazing, but I"m not willing to accept a lot of risk.

Cindy

The most bothersome symptoms of HPP for me are pain, fatigue, muscle weakness and the unpredictability of how those symptoms change from day to day. HPP has a huge impact on my daily life. Some days I cannot wash my own hair in the shower because of the pain and fatigue.Honestly, I only shower when I absolutely have to these days. I have to use a shower chair. My husband must assist me in and out of the bath tub if I want to soak in epsom salts to help alleviate pain. I can no longer do heavier cleaning on the house. I physically can't do yard work or even tend to the flower beds. Lately, I don't even have enough grip strength to open a bottle of water on my own.I can no longer grocery shop unassisted. I just ride around in a scooter and instruct whoever I can find to go with me what to get. Some days I'm too exhausted to even walk from the handicap spot to the door to see if a scooter is available and just send them in with the list. I'm currently on Strensiq. Before Strensiq, I was basically bed/chair ridden and scooter bound. I am up and about now and things were much better before a cardiac cath that went horribly wrong and major vascular injury and reconstructive surgery. It's still being debated if my calcium buildup in my cardiovascular system is from HPP dumping calcium in soft tissue/not getting filtered out of the blood effectively due to my kidney disease secondary to HPP or if I have some type of genetic lipid disease as well contributing to those issues. I hope a new therapy wouldn't cause lipodystrophy and wouldn't be so painful during injection. If they could figure out what causes the muscle weakness, fatigue and neuro issues and target those symptoms as well with treatment that would be wonderful. When I started the Strensiq trial, I was willing to risk my life. I did not want to live any longer the way I was.I had prayed for a doctor like Dr. House on the TV show.

Cure me or kill me. I didn't care at that point but one needed to happen. Luckily I was accepted into the trial and I started seeing minor improvements, then some major improvements, then heart attack #3 happened that caused major setbacks with the vascular mess. At this point, I can't say I'm willing to risk my current health situation getting worse (or my life) but I'm also on a quest to make things better for my children and grandchildren that struggle with HPP themselves. So it really just depends on what the potential new treatment is expected to do.If it's a potential cure like gene editing, I might be game. The grandkids (and their future kids) could benefit tremendously from that. If it's the same type of enzyme replacement with tweaks to fix the other symptoms, I'd probably be game to risk my current status short term, knowing I could withdraw from a trial if I regressed quickly. If it's something completely new and unknown, I would give it some thought, but can't promise I'd accept any major risks or set backs.

Stephen

What went into your decision to discontinue using Strensiq?"

1. Average ALP level trended significantly downward over time:

For example, my average ALP during year one of Strensiq therapy was 7082 U/L (95% confidence interval: 6015 – 8149 U/L). During year two of Strensiq therapy, my average ALP dropped by 1443 U/L (same sample size), with a 95% confidence interval of 4735 – 6544 U/L.

Additionally, my maximum ALP achieved during year one of was 9594 U/L, with a minimum of 5004 U/L. Year two maximum: 8057 U/L, minimum, 4000 U/L.

2. A significant decrease (as a trend) in the average estimated glomerular filtration rate (eGFR) may indicate waning Strensiq efficacy due to the development of nephrolithiasis and/or increased renal blood pressure (renal hypertension). The eGFR is routinely derived in lab tests as a function of serum creatinine.

For example, during year one of Strensiq therapy, my average eGFR increased by a remarkable 19%, from 76.6% pre-Strensiq to 95.5%. During year two, my average eGFR *decreased* by nearly the same percentage, from 95.5% to 74.7%, or around 21%.

3. Biomarkers of bone turnover remained stagnant throughout treatment.For example, my serum P1NP never got higher than 27 mcg/L, and my serum osteocalcin never got higher than 11 ng/mL, both indicators that little to no bone formation/metabolism occurred throughout the entirety of treatment with Strensiq. Seefried et al. (2021) found that adult patients on Strensiq typically experience increases in bone turnover as part of overall bone mineralization improvement. I did not.

4. Persistent HPP symptoms. While Strensiq seemed to improve my mental health to an extent, it never had a definitive impact on my musculoskeletal health. I continued to experience significant, non-healing metatarsal stress fractures throughout treatment, chronic pain, chronic fatigue, and muscle weakness, as well as peripheral neuropathy.

Christine

My identical twin and I are both diagnosed with HPP. I was approved for Strensiq and she was not. We have different insurances. She has the exact same mutation but cant get the medication to help her but i can. Not Fair.

Also, i have to wait at least 6 mos. for an appt for my daughter to see a geneticist when i know she has HPP and would benefit from Strensiq. There should be a better way to streamline the process. This is my daughter Morgan
https://softbones.org/patient-of-the-month-morgan-s/

Barbara

Even though I know it is not an adversarial relationship, every year I feel I am fighting with my insurance company to get the coverage I need for my medication. What part of GENETIC do they not understand. Yes, this is frustrating when I must jump through the hoops once again to provide the medical history along with lab testing just like I provided every year before. I know that Strensiq is one of the most expensive drugs but it is also the ONLY drug for treating my rae disease. And, yes I am once again immersed in the drug approval process for the drug I have been on for nearly 12 years with excellent results.

Judith

I am a patient with mild-moderate HPP. I have the most common symptoms associated with the disease, primarily musculoskeletal pain resulting from severe arthritic joints and CPPD. Muscle weakness, dentition abnormalities, fatigue, anxiety and brain fog have also been bothersome. Since diagnosis, I have been fortunate to have access to knowledgeable and open-minded physicians who have helped me get treatment with Strensiq and manage my pain. Strensiq has helped tremendously with musculoskeletal weakness and fatigue.I am much more physically active than pre-treatment and it has improved my QOL and overall health tremendously. After experimentation, musculoskeletal pain is kept under control by a combination of different medications. Strensiq cannot undo the damage already done to the joints. More than anything, I hope that screening for HPP will be performed in all infants so that it doesn't take decades for patients (especially those with initially more subtle symptoms), to be diagnosed and followed/treated. If I had been diagnosed as an infant (first symptoms for me was hip disclocation at birth), I potentially could have avoided multiple fractures, CPPD and resulting degeneration of shoulder, wrist, knee and feet joints. The ideal therapy would be to correct the ALPL gene and allow for normalization of TSALP levels so that the systemic manifestations of the disease could be avoided for all HPP patients. Personally, I would happily risk participation in any first-in-man study if it could possibly result in an efficacious therapy for the HPP community.

Jennifer

My child was dx at 2 months old. We started treatment this summer - she is now 6 years old. We wanted more data and long-term side effect data. Our biggest struggle is giving her the injections and the impact of the act of injections on our entire young family. I am often the only adult in my household with a husband who travels out f state frequently for work. I cannot administer her treatment with out one or two other adults holding her down.Her siblings watch us in horror as we have to pin their screaming sister in order to administer medication. The trauma as parents having to use these methods because she is old enough to understand that shots are not something that her peers or her siblings experience. The realization that her condition is not something mom and dad say in passing, it is a real situation made even more real by the act of a shot in her body multiple times a week - for life. The realization that we as parents, will never be able to leave her in the care of someone else so that we can take a vacation or mental break from the heaviness of these treatments. This is hard emotionally on so many levels. For our family specifically, it is bringing up every traumatic moment of my pregnancy and early HPP diagnosis, and the years of us trying to determine if and when we would start treatment.
What are you doing to research and create other methods of treatment that are not as traumatic for our younger patients and the families who have to administer treatment?

Nele

HPP affects me in almost every aspect of my life. I deteriorate at a steady rate. The fatigue gets worse every day and the bone pains can get very intense. I don't mind the fractures as much, as you can treat those and have a certain time table on them. The rest of the symptoms are however - in Belgium - not treated and patients are left on their own. In the past 5 years I have gone from being able to hike 5 kilometers to not being able to walk 500 meters now and being in a wheelchair parttime. That, mixed with the horrid fatigue is such a drain on my life that I survive, and am unable to live. As a single perosn, I have to work fulltime but due to HPP I have no life outside of that. My free time is entirely used up by HPP.
I would like to see Alexion work closer with European governments to be able to distribute the meds we need at a fair price. Right now, we are - literally- being left to die because Alexion does not want to conceed to European price norms.
If there were an other therapeutic improvement available but in testing, I would accept the risk. The life I have now is no life at all.

Ashley

My husband has HPP and once Strensiq became available it was a huge relief for our family to finally have a treatment instead of a response. The ongoing concerns we have are around the continuing development of therapies and the means by which they're administered. I would prefer more non-invasive options but I know he would be willing to weigh the pros and cons of something more invasive if it offers prolonged relief. We are always most concerned about maintaining a quality of life for my husband as he manages his HPP. Our hope is he continues to have the ability to participate in our kids' lives without difficulty or outright exclusion due to a lack of care.

Michelle

Most bothersome & greatest impact- achiness and frightful to do activities that I used to love, but now fear the aftermath of having to rest for 1-2 days afterward. Feeling dehydrated and exhausted, but all of my blood work is perfect.

The most frustrating thing is that I can't find a doctor who understands HPP. My doctor calls me a mystery when I tell her my symptoms.

I am very grateful to the softbones.org group and Sue for all of the resources and for making me feel not alone during these adjustments.

Stephen

The following are proposed critical components of any hypophosphatasia (HPP) treatment modality:

- Biochemical

- Normalizes urine calcium levels to reduce the probability of nephrolithiasis.
- Increases (to a therapeutic limit) levels of B6 vitamers in cerebral spinal fluid (permitted by the commensurate decrease in plasma PLP) as measured by a spinal tap (Wright et al. 2020).
- Minimizes the probability of neutralizing antibody development by proper epitope selection, such that fewer than 25% of those in forthcoming clinical trials develop said antibodies (versus 71% cited in adults with Strensiq in clinical trials prior to 2015).

- Musculoskeletal

- Decreases all-fracture occurrence by at least 50% versus the typical baseline observed from the pediatric to adult HPP population.
- Decreases fracture healing time by an average of 2 weeks via bone turnover/metabolism improvements.
- Decreases chronic pain as measured by standard pain scales, and via reduction of the need for opioid pain medication, NSAIDs, and other pain management modalities.
- Reduces the frequency of subcutaneous injection site reactions (ISRs) by one of the following methods:

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(1) The reduction of the current phosphate buffer concentration from 25.68 mM per vial (as both monobasic and dibasic phosphate) to < 10 mM per vial (Usach et al. 2019).

(2) The choice of a different buffer, such as citrate, maintained at a concentration < 7.3 mM (Usach et al. 2019).

o Reduces the probability of extra-cellular calcifications (e.g., ectopic or vascular) by normalizing each patient's BALP (and TNSALP) value (and thus the treatment dose) as a function of his or her body mass index (BMI), his or her optimal BMI, or his/her body body surface area.

* Is a random, extremely high TNSALP (or BALP) value (e.g., > 5000 U/L) safe long-term given the many critical functions of the TNSALP enzyme beyond musculoskeletal health?

* Does a therapeutic "threshold" BALP or TNSALP value exist for each patient, above which clinical benefit diminishes and the probability of ectopic or vascular calcifications, neurological deficits, or other side effects increases?

* Could finding a therapeutic ALP threshold also normalize Strensiq's neurological influence? For example, the ALP substrate PLP may not fall to sub-normal levels, such that peripheral neuropathy or other neurological deficits related to Vitamin B6 deficiency develop.

* These symptoms have been anecdotally observed in numerous Strensiq patients and facilitated many discussions about the utility and efficacy of pyridoxine supplementation during treatment.

- Neurological

o Increases levels of cerebral spinal fluid (CSF) dopamine, norepinephrine, and serotonin. These neurotransmitter levels are directly a function of upstream B6 vitamer levels (Wright et al. 2020).

* With an individualized, therapeutic serum TNSALP (BALP) level established for each patient, the CSF B6 level would (ideally) be optimized, perhaps permitting commensurate mental health improvements (especially anxiety and depression) over a period of several months, akin to the time it takes antidepressants and other psychiatric medications to start showing complete therapeutic benefit.

- Improves cognition (often referred to as "brain fog" within the HPP community) by safely increasing levels of CSF dopamine and norepinephrine. Increases in these two neurotransmitters may also improve concentration, or "ADHD-like" symptoms that are frequently mentioned by HPP patients (Colazo et al. 2019).
- Decreases chronic fatigue, again via safe elevations in CSF B6 vitamers and downstream upregulation of dopamine and norepinephrine.

Sadie

The most frustrating symptom of having HPP is overwhelming fatigue.

Stephen

Strensiq routinely interferes with immunoassays that employ alkaline phosphatase (ALP) as their conjugate during the "washing step" of the assay execution procedure. While not all immunoassays are subject to this interference, and the chemistry of the interference is still the subject of ongoing research, there is published and empirical documentation illustrating this phenomenon in a variety of lab tests, especially in the endocrine realm.

I was a Strensiq patient from 2015-2017, but ultimately failed to respond to treatment during year two after evidence of response during year one. While on treatment, the first lab interference experience I had involved total and free testosterone as tested via ELISA at Nebraska Medicine.Strensiq rendered both values undetectable every instance they were measured, and after having stopped treatment for an extended period in late 2017, both values returned to normal.

These findings were formally published by Sonfronescu et al. (2018): https://www.sciencedirect.com/science/article/abs/pii/S0009912017310688?via%3Dihub.

Throughout the aforementioned authorship process, I was *also* hospitalized on separate occasions for elevated cardiac troponin I (cTn1) values, with no ischemic findings ever noted even following a cardiac catheterization procedure.

My clinical geneticist decided to run an (informal) experiment to ascertain (irrefutably) if the three hospital admissions were unnecessary because of *false positive* cTn1 values due to Strensiq interference.

On 12/9/2016 (see below), I had cTn1 performed again at UNMC, with two other blood samples drawn at the same time sent to labs that perform the cTn1 assay differently, without ALP involvement (LabCorp Denver and Focus Technologies). The results are as follows, with my UNMC hospital results also included: